File No. CT-2023-007

COMPETITION TRIBUNAL

IN THE MATTER OF the *Competition Act*, R.S.C. 1985, c. C-34 (the "**Act**");

AND IN THE MATTER OF an application by Apotex Inc. for an order pursuant to section 103.1 of the Act granting leave to bring an application under section 79 of the Act;

AND IN THE MATTER OF an application by Apotex Inc. for an order pursuant to section 79 of the Act;

BETWEEN:

APOTEX INC.

Applicant

– and –

PALADIN LABS INC., ENDO PHARMACEUTICALS INC., TAKEDA CANADA INC., and TAKEDA PHARMACEUTICALS U.S.A. INC.

Respondents

AFFIDAVIT OF NICK BOORMAN

(Pursuant to section 103.1 of the *Competition Act*)

I, NICK BOORMAN, of the City of Toronto, in the Province of Ontario, **MAKE OATH AND SAY**:

1. I am employed by Apotex Inc. ("**Apotex**") as Vice-President, Marketing & Commercial Operations, and as such I have personal knowledge of the matters herein deposed, except where I rely on information provided by other persons, in which case, I believe that information to be true.

2. This affidavit is sworn in support of an application being brought by Apotex for an order pursuant to section 103.1 of the *Competition Act* ("**Act**") for leave to bring an application against Respondents under section 79 of the Act.

I. CURRICULUM VITAE

3. I was originally hired by Apotex in 2009. Since that time, I have been employed in a number of increasingly senior marketing and commercial roles at Apotex. My responsibilities have included overseeing analysts responsible for sales forecasts, the oversight of the evaluation of potential new products for financial opportunity, and the oversight of commercial planning for new products that Apotex has decided to launch. At present, I am responsible for overseeing Apotex's marketing and commercial operations in Canada. These responsibilities include overseeing new product development and new product launch. I report directly to Mr. Ray Shelley, who is the President of Apotex's operations in Canada.

4. My responsibilities include the oversight of the Apotex products described in this affidavit.

5. I hold a Bachelor of Commerce degree from the University of Toronto and a Master of Business Administration degree from York University.

II. THE PARTIES

6. Apotex is a company incorporated under the laws of Ontario. Apotex produces high-quality, affordable medicines (both generic and branded drugs). For nearly 50 years, Apotex has pursued a business strategy of challenging third parties' drug patents in Canada in order to launch new drugs before the expiry of those patents, competing vigorously with Apotex's rivals (including

brand and generic pharmaceutical companies) and providing affordable, innovative and high quality solutions to Canadians. Apotex's efforts have made hundreds of drugs available at lower costs, saving Canadian patients and taxpayers billions of dollars.

7. Takeda Pharmaceutical Company Limited ("**TPCL**") is a Japan-based pharmaceutical company. I have attached to this affidavit as Exhibit "1" a copy of TPCL's Annual Report for the fiscal year ended March 31, 2023. As set out on page F-74 of Exhibit 1, the Respondents, Takeda Pharmaceuticals U.S.A. Inc. ("**Takeda US**") and Takeda Canada Inc. ("**Takeda Canada**"), are each wholly-owned subsidiaries of TPCL. Takeda US and Takeda Canada market branded drugs.

8. I have attached to this affidavit as Exhibit "2" a copy of Endo International plc's Annual Report for the fiscal year ended December 31, 2022. As set out at *exhibit 21.1 (Subsidiaries of the Registrant)* of Exhibit "2", the Respondents, Endo Pharmaceuticals Inc. ("**Endo**") and Paladin Labs Inc. ("**Paladin**"), are each subsidiaries of Endo International plc. To the best of my knowledge, Endo markets both generic and branded drugs. Paladin is a Canadian-based pharmaceutical company that I understand, among other things, imports and distributes drugs on behalf of third parties.

III. THE REGULATION OF DRUGS IN CANADA AND THE PROVINCES

9. In order for Apotex (or any other drug company) to launch a drug, it must first obtain a Notice of Compliance ("**NOC**") from the Minister of Health ("**Minister**"). A NOC for a new drug is obtained by first filing with the Minister a new drug submission ("**NDS**") or an abbreviated new drug submission ("**ANDS**") under Division 8 of the *Food and Drug Regulations*.

10. Some drug manufacturers employ the NDS route for the purpose of securing a NOC for their new medicinal therapies. In the NDS, the manufacturer includes the required information and data to establish that the submitted product is safe and effective. Drugs that obtain a NOC with an NDS are typically referred to as "branded".

11. Obtaining a NOC by filing an ANDS is typically a shorter process than the NDS route. An ANDS can be utilized if a drug manufacturer can establish that its new product is equivalent in specific ways to a drug for which a NOC has already been issued (the "**Reference Product**"). A drug manufacturer is permitted to file an ANDS where, in comparison with a Reference Product, the manufacturer can demonstrate (i) the new drug is the pharmaceutical equivalent of the Reference Product (i.e., it has the same "active ingredient"); (ii) the new drug is bioequivalent to the Reference Product, based on the pharmaceutical characteristics (i.e., the "bioavailability" of the generic drug after administration to a patient is the same as the Reference Product); (iii) the route of administration of the new drug is the same as the Reference Product; and (iv) the conditions of use of the new drug fall within the conditions of use for the Reference Product. Drugs that obtain a NOC via an ANDS are typically referred to as "generic drugs" or "generics".

12. From time to time, Health Canada requests that a manufacturer establish a Risk Management Plan ("**RMP**") for a drug, including for a drug with a new active ingredient. While each RMP is different, a RMP will typically restrict the distribution of and access to a drug to prevent adverse effects or other drug-related problems.

13. I have attached to this affidavit as Exhibit "3" a copy of a public statement made by Health Canada in August 2020 entitled, "Notice of clarification to drug manufacturers and sponsors –

Risk Management Plans – Update". That public statement includes the following:

> This notice is being issued to clarify to drug manufacturers and sponsors that elements of Risk Management Plans (RMPs) required by Health Canada, such as controlled distribution programs, are not intended to restrict access to Canadian Reference Products (CRPs) for generic drug manufacturers for the purposes of conducting comparative testing. Any RMP elements should not delay or hinder comparative testing with generic products or hinder their ability to enter the market.
>
> …
>
> Health Canada is committed to making sure that RMPs continue to contribute to patient safety. It also reminds sponsors that RMP elements should not be seen as a reason to delay or stop comparative testing with generic products, or to prevent them from entering the market.

14. I attach to this affidavit as Exhibit "4" a document published online by the Competition Bureau in December 2018 entitled, "Competition Bureau Position Statement, Investigation into alleged practices of Celgene, Pfizer and Sanofi". That document includes the following:

> Without access to CRPs a Generic cannot conduct bioequivalence testing, and therefore in many cases cannot receive the necessary regulatory approval to market the generic drug. As a result, if a Brand can prevent or delay Generics from accessing CRPs, this may limit competition from Generics and deny Canadians timely access to safe and effective generic drugs at lower prices.
>
> …
>
> Based on the information gathered in the course of the Inquiry, the Bureau found that Generics have indeed requested CRPs directly from Celgene on more than one occasion. However, the Bureau is not aware of any instance where a request for restricted CRPs has been fulfilled by Celgene due to various reasons. In at least one case, Celgene has imposed conditions on the supply to a Generic, which the Generic has characterized as unnecessary and burdensome.
>
> While these requests remained unfulfilled by Celgene, the Bureau was made aware of the fact that certain Generics were ultimately able to obtain sufficient CRPs through other means. The Bureau's decision to discontinue its investigation against Celgene turned on this fact as well as on the fact that these Generics were eventually able to conduct the necessary studies to make the submissions needed for Health Canada approval.

15. I attach to this affidavit as Exhibit "5" a document a document published online by the Competition Bureau in April 2020 entitled, "Competition Bureau statement regarding its inquiry into alleged anti-competitive conduct by Otsuka". That document includes the following:

> As discussed further in the 2018 Position Statement, without access to brand samples, a Generic cannot conduct bioequivalence testing, and therefore in many cases cannot receive the necessary regulatory approval to market the generic drug. As a result, if a branded drug manufacturer can prevent or delay Generics from accessing these samples, it can limit competition from Generics.
>
> Generics generally rely on the clinical testing that the Brand had conducted to prove the drug was safe and effective, resulting in significant cost savings. This allows Generics to compete with Brand drugs with lower prices. In an effort to balance the incentives of Brand drugs to innovate with the benefits of Generic competition, the Bureau is committed to taking appropriate action to prevent practices by Brand drugs that aim to prevent Generics from competing in the market.
>
> The Bureau re-emphasizes its serious concerns with this conduct and its commitment to addressing these concerns. This matter was ultimately resolved shortly after the Bureau became involved (but approximately one year after the Generic first requested samples). Following Otsuka's supply of Jinarc to the Generic subsequent to the Bureau's intervention and upon being satisfied that the supply had been delivered, the Bureau discontinued its inquiry. Despite this outcome, the Bureau remains very concerned with the course of conduct that is being repeated in the industry.
>
> The Bureau will continue to monitor the pharmaceutical industry for any conduct that prevents or delays the supply of samples of branded drugs to Generics. As this is now the second time the Bureau has provided guidance to the industry on this issue, branded drug manufacturers should be aware that in future even if samples are eventually supplied, the Bureau will take the necessary steps to address past conduct, including seeking administrative monetary penalties, where the evidence establishes the Act is engaged. Given this guidance from the Bureau and the guidance discussed below from Health Canada, branded drug manufacturers should anticipate that the Bureau will treat any explanation for a failure to supply Generics in a timely manner with an extremely high degree of skepticism.

16. Generic drugs are typically sold at a price that is significantly lower than the price of the branded version of the same product (i.e., the Reference Product). To lower the costs of drugs for patients and payors (including insurance companies and provincial governments), I am aware that

Canadian governments maintain rules that, with some exceptions, require a pharmacist to dispense a generic drug when the pharmacist is presented with a prescription for a branded drug (a practice commonly referred to as "automatic substitution"). Due to the lower prices of generic drugs and the automatic substitution rules, the first generic product to enter a market typically captures a significant share of the market quickly upon its launch.

IV. ICLUSIG (Ponatinib)

17. I am aware that ponatinib hydrochloride ("**ponatinib**") is an anticancer drug that is indicated for the treatment of two types of leukemia: chronic myeloid leukemia ("**CML**") and Philadelphia chromosome positive acute lymphoblastic leukemia ("**Ph+ ALL**"). Ponatinib is from a class of drugs called "tyrosine kinase inhibitors" ("**TKI**"). I am aware that patients with CML and Ph+ ALL experience uncontrollable growth of certain blood cells, and that TKIs slow or stop this uncontrolled growth, significantly improving outcomes for patients with these types of leukemia.

18. I have attached to this affidavit as Exhibit "6" a print-out from Health Canada's online Notice of Compliance database, which shows that Takeda US holds a NOC for the drug product ICLUSIG. Ponatinib is the active medical ingredient in ICLUSIG.

19. Exhibit "6" also indicates that NOCs for a ponatinib hydrochloride formulation were earlier issued to a company known as Ariad Pharmaceuticals Inc. I have attached as Exhibit "7" a press release from 2017, issued by TPCL, announcing its acquisition of Ariad Pharmaceuticals Inc.

20. I have attached to this affidavit as Exhibit "8" the product monograph for ICLUSIG. As set out on page 1 of Exhibit "8", Paladin is the importer and distributor of ICLUSIG for Canada.

21. Page 2 of Exhibit "8" contains the following:

> ICLUSIG (ponatinib tablets) is indicated for:
>
> - the treatment of adult patients with chronic phase (CP), accelerated phase (AP), or blast phase (BP) chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom other tyrosine kinase inhibitor (TKI) therapy is not appropriate, including CML or Ph+ ALL that is T315I mutation positive or where there is prior TKI resistance or intolerance.

22. Page 7 of Exhibit "8" contains the following:

> **4.2 Recommended Dose and Dosage Adjustment**
>
> **CP-CML**
>
> The recommended starting dosage of ICLUSIG is 45 mg orally once daily with a reduction to 15 mg orally once daily upon achievement of molecular response (≤1% BCR-ABL1IS). Patients with loss of response can re-escalate the dose of ICLUSIG to a previously tolerated dosage of 30 mg or 45 mg orally once daily. Continue ICLUSIG until loss of response at the re-escalated dose or unacceptable toxicity. Consider discontinuing ICLUSIG if hematologic response has not occurred by 3 months.
>
> **AP-CML, BP-CML, and Ph+ ALL**
>
> The recommended starting dosage is 45 mg of ICLUSIG once daily. Continue ICLUSIG until loss of response or unacceptable toxicity. Consider reducing the dose of ICLUSIG for patients with accelerated phase (AP) CML who have achieved a major cytogenetic response. Consider discontinuing ICLUSIG if response has not occurred by 3 months.

23. I have attached to this affidavit as Exhibit "9" a print-out from the Health Canada Drug Product Database for ICLUSIG retrieved September 28, 2023, which shows that, at present,

ICLUSIG is exclusively marketed in Canada in 15 mg tablets, and that product has Drug Identification number (DIN) of 02437333.

24. I understand that Health Canada requested a Risk Management Program for ICLUSIG. I have attached to this affidavit as Exhibit "10" a print-out from the ICLUSIG Controlled Distribution Program ("**CDP**") website maintained by Paladin retrieved September 28, 2023. That document includes the following:

> **ICLUSIG CONTROLLED DISTRIBUTION PROGRAM (CDP)**
>
> Paladin Labs Inc. would like to inform you about the ICLUSIG Controlled Distribution Program.
>
> This controlled distribution program has been determined by Health Canada to be required for ICLUSIG to ensure that the benefit of the drug outweighs the risks of vascular occlusion and congestive heart failure.
>
> - Only prescribers who are certified in the ICLUSIG Controlled Distribution Program can prescribe ICLUSIG.
> - Prescribers must read the ICLUSIG Product Monograph and the ICLUSIG Medication Guide, review the ICLUSIG Educational Slide Set, and pass the Knowledge Assessment at the end of the Slide Set.
> - Prescribers must review the ICLUSIG Medication Guide with patients who are initiating ICLUSIG treatment. After the review, the prescriber and the patient must sign the Patient Informed Consent Form. A signed copy of the form will be maintained by the prescriber in the patient's chart, and a signed copy will be provided to the patient.
> - Only pharmacies that agree to follow the ICLUSIG Controlled Distribution Program requirements will dispense ICLUSIG.
> - Pharmacies will only dispense an ICLUSIG prescription after verifying that the prescriber is certified in the ICLUSIG Controlled Distribution Program.

25. As set out on page 63 TPCL's Annual Report for the fiscal year ended March 31, 2023, attached as Exhibit "1", TPCL reported global revenues of JPY ¥47.2 billion from the sale of

ICLUSIG for the fiscal year ended March 31, 2023 (equivalent to approximately CAD $480,496,000 based on the Bank of Canada daily exchange rate for March 31, 2023).

26. With respect to sales of ICLUSIG in Canada, I have attached as Exhibit "11" data obtained by Apotex from the health data company IQVIA Inc. ("**IQVIA**"). Apotex regularly purchases data and information from IQVIA in the ordinary course of business. Apotex has found IQVIA data and information to be reliable, and Apotex relies on IQVIA data and information in making business decisions. As set out in Exhibit "11", IQVIA reports sales of ICLUSIG in Canada in 2022 of CAD $8,210,594. IQVIA further reports that these sales were generated from the sale of approximately 51,900 doses of ICLUSIG. This implies an average sale price per dose of CAD $158.20.

27. I am aware that Health Canada requires that manufacturers report actual and anticipated shortages of drugs. Those reports are publicly accessible on the Drug Shortage Canada website operated by Bell Canada under contract with Health Canada. I have attached as Exhibit "12" a print-out from the Drug Shortages Canada retrieved September 28, 2023**,** which indicates that there is no report of any actual or anticipated shortage of ICLUSIG.

V. APOTEX'S BUSINESS PLAN FOR A PONATINIB PRODUCT

28. In the normal course of business, Apotex surveys patent-protected drugs marketed in Canada. In many cases for an individual drug, Apotex assesses whether there is an opportunity to develop a generic version of that drug, successfully challenge the validity or application of any patent that is listed in respect of the drug, and launch a generic version of the drug to compete against the higher priced branded product, all while still earning a profit for Apotex and making

affordable medicines available for the Canadian public. Apotex often concentrates its new drug development efforts on those products that Apotex believes present the most attractive profit opportunities, and the greatest savings for Canadians.

29. To evaluate the potential profitability of a new product, Apotex business people utilize a proprietary forecasting model. Apotex developed and calibrated this model based on nearly 50 years of experience developing and launching hundreds of generic drugs. The model requires a number of inputs, including: (i) data about the number of doses sold, disaggregated by province, sales channel (hospital vs. retail), format and other factors; (ii) data about the branded drug company's estimated revenues for the drug product, disaggregated in the same manner; (iii) data about the per dose price charged by the branded drug company; (iv) data about the expiry date of any patents listed in respect of the product; (v) information about whether the price of the drug is reimbursed by the various provincial governments' drug benefit plans; (vi) estimates of Apotex's upfront costs to develop the drug (including the cost involved in conducting a bioequivalence study, preparing an ANDS, responding to any comments from Health Canada, and litigating any patents asserted by the branded drug company); (vii) estimates of Apotex's unit costs to manufacture, package, distribute and market its drug product; (viii) an estimate of how many other generic drug companies might come to market with a competing version of the drug (including when each of those companies might commence sales); (ix) estimates of the rate of "penetration" that generic products can expect to achieve in each province; and (x) estimates of the share of generic sales that Apotex can expect to achieve in each province.

30. With these (and other) inputs, the model generates a series of outputs, including an estimate of: (i) the number of doses that Apotex expects to sell in each of the first five years after the launch of a new product; (ii) the price at which Apotex expects to sell those doses, (iii) the revenue and profit that Apotex expects to earn from those sale, and (iv) how market-wide demand is likely to evolve in each year (e.g., whether total sales volumes will increase or decrease). The model can then be re-calibrated by adjusting the inputs, to test whether the product would be profitable for Apotex in a number of realistic scenarios.

31. Apotex utilizes the outputs of the forecasting model to support critical business decision-making in the normal course of business, including decisions about which drugs Apotex ought to invest in and develop.

32. Utilizing its forecasting model, Apotex examined the profit opportunity associated with the launch of a generic ponatinib product. Apotex business people supplied the model with the inputs described above. The inputs included a number of conservative assumptions, including [redacted] The effect of this conservative approach is to lower the model's estimate of Apotex's future sales volumes, price, revenues and profit.

33. A copy of the model used to evaluate ponatinib is attached as Exhibit "13". Among other things, the model forecast the following:

a. at tab "12M Summary", cells B26 to B30 of Exhibit "13", growth in total sales of ponatinib (comprising all products, including ICLUSIG and generic versions) after

launch of Apotex's generic product of [redacted] in the first year, [redacted] in the second year and further growth in subsequent years;

b. at tab "Post-L 5YR Summary (New)", cells B59, B70 and B71 of Exhibit "13", [redacted] Apotex is likely to sell more than [redacted] doses and capture between [redacted] and [redacted] of the market (by volume) in the first year after launch;

c. at tab "Post-L 5YR Summary (New)", cell B45 of Exhibit "13", [redacted] Apotex is likely to sell its product in the first year after launch for a blended price of [redacted] per dose (representing a discount of more than [redacted] off of Paladin's current price for ICLUSIG); and

d. at tab "Post-L 5YR Summary (New)", cells B88 and B97 of Exhibit "13", [redacted] Apotex is likely to generate revenues of more than CAD [redacted] million and gross margins of more than CAD [redacted] million in the first year after launch.

34. In reliance upon this information, Apotex's senior managers approved the development of a new generic ponatinib product.

35. Apotex has taken a number of business steps associated with the development of its ponatinib business. For example, Apotex prepared a detailed protocol for the conduct of a study of the bioequivalence of Apotex's generic ponatinib product and ICLUSIG. I have attached to this

affidavit as Exhibit "14" a copy of Apotex's finalized protocol for the conduct of a study of the bioequivalence of Apotex's generic ponatinib product and ICLUSIG. The next step Apotex must take in the development of its ponatinib business is to conduct and complete a bioequivalence study. This requires that Apotex obtain a small sample of ICLUSIG. Apotex cannot file its ANDS (or obtain a NOC, or launch its product, or compete against Takeda US and Paladin) until the bioequivalence study is complete.

VI. APOTEX'S ATTEMPTS TO OBTAIN A SAMPLE OF ICLUSIG

36. In 2023, Apotex attempted to obtain a small supply of ICLUSIG from numerous different intermediaries in the pharmaceutical industry in Canada and outside Canada. I understand that in each instance, the intermediary was unwilling or unable to supply the requested ICLUSIG to Apotex.

37. I have attached to this affidavit as Exhibit "15" a copy of Apotex's email correspondence with [redacted] drug supplier. That exhibit includes the following correspondence:

a. May 8, 2023 – Apotex writes to [redacted], "Could you please provide price and availability of ICLUSIG Canada – DIN 02437333."

b. May 8, 2023 – [redacted] replies to Apotex, "Currently we don't have any access on ICLUSIG Canada."

38. I have attached to this affidavit as Exhibit "16" a copy of Apotex's email correspondence with [redacted] drug supplier. That exhibit includes the following correspondence:

a. May 8, 2023 – Apotex writes to [redacted], "Could you please provide price and availability of ICLUSIG Canada – DIN 02437333."

b. May 12, 2023 – [redacted] replies to Apotex, "Unfortunately we cannot assist on this one as we do not currently have access to the product."

39. I have attached to this affidavit as Exhibit "17" a copy of Apotex's email correspondence with [redacted] drug supplier. That document contains the following correspondence:

a. May 8, 2023 – Apotex writes to [redacted], "Please provide price and availability of Iclusig Canada."

b. May 11, 2023 – [redacted] replies to Apotex, "Not able to get this one."

40. I have attached to this affidavit as Exhibit "18" a copy of Apotex's email correspondence with [redacted] drug supplier. That document contains the following correspondence:

a. May 8, 2023 – Apotex writes to [redacted], "Please provide price and availability of Iclusig Canada."

b. May 8, 2023 – [redacted] replies to Apotex, "Sorry, no access for the requested product."

41. In light of its inability to acquire ICLUSIG from third parties, on June 12, 2023, an Apotex employee wrote to Takeda US and Paladin by courier, requesting the supply of ICLUSIG. Apotex

requested a supply of 360 tablets of ICLUSIG. Apotex's letter expressly advised that the purpose of the request was to use the supply as a Reference Product to conduct a bioequivalence study. I have attached to this affidavit as Exhibit "19" a copy of that letter. I am advised that Apotex did not receive any reply.

42. On August 24, 2023, an Apotex employee Adam Rambert, Assistant General Counsel, Canada & ROW of Apotex wrote to Takeda Canada, Endo and Paladin by courier and email, repeating Apotex's request for the supply of a small volume of ICLUSIG in connection with Apotex's efforts to demonstrate bioequivalence and launch a generic version of ICLUSIG. I have attached to this affidavit as Exhibit "20" a copy of that letter. That letter contains the following:

> So as not to delay any further Apotex's efforts to develop and launch a generic version of Iclusig®, we require a response to this letter within 5 business days, and for the requested supply of Iclusig® to be delivered to Apotex within 20 business days of this letter.
>
> 20 business days from the date of this letter is sufficient time to settle all reasonable supply and other terms, and to deliver the product. Apotex is prepared to work quickly in cooperation with you to permit delivery within this time frame. Accordingly, in your initial reply to this letter, please include (i) the standard supply terms that apply to the supply of a small volume of Iclusig® to an experienced generic pharmaceutical company such as Apotex, (ii) the desired pricing terms for the requested supply of Iclusig®, (iii) the payment terms and instructions (e.g., wire transfer instructions), (iv) if delivery will not be made to Apotex's offices as requested in the June 12 letter, any relevant information about the manner and place of delivery of the requested supply of Iclusig® (so that Apotex may make appropriate arrangements) and (v) any other commercially reasonable matters. Apotex is prepared to agree to reasonable commercial terms for the supply of a small amount of reference product. However, unreasonable requests that are not commercially practicable, but that are instead intended to delay the supply of the requested product, will not be honoured.
>
> Health Canada and the Canadian Competition Bureau have each explained the importance of generic pharmaceutical companies being able to obtain prompt access to reference products for comparative testing purposes. Both agencies have

also explained that Risk Management Plans and other aspects of the regulation of pharmaceutical products should not delay the supply of drugs.

43. On September 8, 2023, Alex Nikas, Vice President & Associate General Counsel Global Ops and R&D at Endo wrote to Mr. Rambert at Apotex via email. I have attached to this affidavit as Exhibit "21" a copy of that email. That email (i) confirmed that Endo and Paladin are affiliated; (ii) confirmed that Paladin distributes ICLUSIG in Canada; (iii) advised that Endo and Paladin had conferred with Takeda US and Takeda Canada about Apotex's request; and (iv) directed Apotex to contact Paladin's customer service department to establish an account and place an order for ICLUSIG.

44. On September 8, 2023, Mr. Rambert of Apotex of wrote to Paladin's customer service department to establish an account and place an order for ICLUSIG. I am advised by Mr. Rambert that no response was received to that email. I am informed that on September 15, 2023, Mr. Rambert repeated Apotex's request to Paladin. I understand that Paladin did not respond until Paladin sent a response on September 17, 2023. I have attached to this affidavit as Exhibit "22" a copy of that correspondence.

45. I am informed that, since that time, Paladin has, in correspondence with Mr. Rambert, offered multiple reasons that are in my view implausible for why ICLUSIG cannot be supplied or cannot be supplied expeditiously, and requested that Apotex participate in a series of tasks that I do not consider to be commercially reasonable. For example:

a. I have attached to this affidavit as Exhibit "23" a copy of an email thread among Apotex, Endo, Paladin, Takeda US and Takeda Canada that is a continuation of the email thread from Exhibit "21". In that email thread, Paladin asserts in emails to

Mr. Rambert from Isabelle Trempe, Vice President, Commercial Operations / Market Access of Paladin (September 17, 2023) and Jean De Serres, VP Scientific Affairs and Operations of Paladin (September 18, 2023) that Paladin does not have sufficient stock to supply Apotex or to supply Apotex expeditiously. In my view, this is implausible because Apotex has requested a small quantity of ICLUSIG and there is no actual or anticipated shortage of ICLUSIG in Canada. On September 18, 2023, Mr. Rambert of Apotex asked Ms. Trempe of Paladin whether Paladin would order additional supply from Takeda US, and asked Matthew Castellarin, in-house counsel to Takeda Canada whether Takeda US would ship additional supply to Paladin. I am informed by Mr. Rambert that neither company has responded to Apotex's inquiries and requests.

b. I have attached to this affidavit as Exhibit "24" a copy of an email thread among Apotex, Endo, Paladin, Takeda US and Takeda Canada that is another continuation of the email thread from Exhibit "21". In the email thread of Exhibit "24", Annie Ethier, Associate at Paladin wrote to Mr. Rambert of Apotex on September 19, 2023 requesting that, before completing the transaction, Apotex apply to Paladin for a line of credit. In my view this is commercially unreasonable because Apotex did not request a line of credit, and because Apotex does not require a line of credit to complete the transaction in question. Instead, Apotex has offered to pay for the order on Paladin's publicly listed terms and conditions, or other terms that are commercially reasonable.

c. I have attached to this affidavit as Exhibit “25” a copy of an email thread among Apotex, Endo, Paladin, Takeda US and Takeda Canada that is another continuation of the email thread from Exhibit “21”. In the email thread of Exhibit “25”, Mr. Nikas of Endo suggested to Mr. Rambert of Apotex on September 20, 2023 that Apotex personnel undergo certain training and become certified under Paladin’s CDP before completing the transaction. In my view, this is commercially unreasonable because Apotex is neither a pharmacist nor a prescriber, and is not subject to the requirements of Paladin’s CDP. I also hold that view in light of the public notice issued by Health Canada, which is Exhibit “3”.

46. As is apparent from the correspondence exhibited to this affidavit and discussed in the preceding paragraphs, Respondents have not responded to Apotex's basic requests regarding what price they will charge Apotex for the samples, or regarding when Apotex can expect delivery.

VII. EFFECT ON APOTEX'S PONATINIB BUSINESS

47. At present, Apotex cannot move forward with development of its ponatinib business. To proceed with its bioequivalence study, which is required for the filing of an ANDS, which in turn must be done in order to obtain a NOC to launch its ponatinib product, Apotex first requires a small volume of ICLUSIG. Respondents' refusal to supply ICLUSIG is preventing Apotex's ponatinib business from proceeding with a step that is necessary to be completed so that Apotex can eventually launch its ponatinib product. As described, Apotex expects its ponatinib business to generate revenues of more than CAD [redacted] million and gross margins of more than CAD [redacted] million in the first year after the launch of its product.

SWORN remotely by Nick Boorman, stated as being at the City of Toronto, in the Province of Ontario, before me at the City of Toronto, in the Province of Ontario, on September 29, 2023, in accordance with O. Reg. 431/20, Administering Oath or Declaration Remotely

A Commissioner, etc.
Name: EMILY GROPER
PROVINCE of ONTARIO
while a Student-at-Law
Expires June 2023

Name: Nick Boorman

File No. CT-2023-007

COMPETITION TRIBUNAL

IN THE MATTER OF the *Competition Act*, R.S.C. 1985, c. C-34 (the "**Act**");

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Respondents

AFFIDAVIT OF NICK BOORMAN
(Pursuant to section 103.1 of the Competition Act)

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Lawyers for the Applicant

Exhibit "1"

Form 20-F FY2022

TAKEDA PHARMACEUTICAL COMPANY LIMITED

As filed with the Securities and Exchange Commission on June 28, 2023

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 20-F

☐ REGISTRATION STATEMENT PURSUANT TO SECTION 12(b) OR 12(g) OF THE SECURITIES EXCHANGE ACT OF 1934

OR

☒ ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended March 31, 2023

OR

☐ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from to

OR

☐ SHELL COMPANY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

Date of event requiring this shell company report

Commission file number: 001-38757

Takeda Yakuhin Kogyo Kabushiki Kaisha

(Exact name of registrant as specified in its charter)

Takeda Pharmaceutical Company Limited

(Translation of registrant's name into English)

Japan	1-1, Nihonbashi-Honcho 2-Chome Chuo-ku, Tokyo 103-8668, Japan
(Jurisdiction of incorporation or organization)	(Address of principal executive offices)

Costa Saroukos
1-1, Nihonbashi-Honcho 2-Chome
Chuo-ku, Tokyo 103-8668, Japan
Tel: +81 3 3278-2306
Fax: +81 3 3278-2268
Email: Global.External.Reporting@takeda.com
(Name, Telephone, E-mail and/or Facsimile number and Address of Company Contact Person)

Securities registered or to be registered pursuant to Section 12(b) of the Act:

Title of Each Class	Trading Symbols	Name of Each Exchange On Which Registered
American Depositary Shares Representing Common Stock	TAK	New York Stock Exchange
Common Stock, no par value*		
0.750% Senior Notes due 2027	TAK27	New York Stock Exchange
1.000% Senior Notes due 2029	TAK29	New York Stock Exchange
1.375% Senior Notes due 2032	TAK32	New York Stock Exchange
2.000% Senior Notes due 2040	TAK40A	New York Stock Exchange

* Listed not for trading, but only in connection with the registration of the American Depositary Shares, pursuant to the requirements of the Securities and Exchange Commission

Securities registered or to be registered pursuant to Section 12(g) of the Act:

None

Securities for which there is a reporting obligation pursuant to Section 15(d) of the Act:

None

Indicate the number of outstanding shares of each of the issuer's classes of capital or common stock as of the close of the period covered by the annual report.

139,663,992 ADSs outstanding as of March 31, 2023

1,554,528,812 shares of common stock as of March 31, 2023

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act Yes ☒ No ☐

If this report is an annual or transition report, indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 Yes ☐ No ☒

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every interactive data file required to be submitted pursuant to Rule 405 of Regulation S-T (§232 405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files) Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or an emerging growth company See definition of "large accelerated filer," "accelerated filer," and "emerging growth company" in Rule 12b-2 of the Exchange Act (Check one):

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ Emerging growth company ☐

If an emerging growth company that prepares its financial statements in accordance with U S GAAP, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards† provided pursuant to Section 13(a) of the Exchange Act ☐

† The term "new or revised financial accounting standard" refers to any update issued by the Financial Accounting Standards Board to its Accounting Standards Codification after April 5, 2012

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U S C 7262(b)) by the registered public accounting firm that prepared or issued its audit report ☒

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240 10D-1(b) ☐

Indicate by check mark which basis of accounting the registrant has used to prepare the financial statements included in this filing:

U S GAAP ☐ | International Financial Reporting Standards as issued by the International Accounting Standards Board ☒ | Other ☐

If "Other" has been checked in response to the previous question, indicate by check mark which financial statement item the registrant has elected to follow ☐ Item 17 ☐ Item 18

If this is an annual report, indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act) Yes ☐ No ☒

(APPLICABLE ONLY TO ISSUERS INVOLVED IN BANKRUPTCY PROCEEDINGS DURING THE PAST FIVE YEARS)

Indicate by check mark whether the registrant has filed all documents and reports required to be filed by Sections 12, 13 or 15(d) of the Securities Exchange Act of 1934 subsequent to the distribution of securities under a plan confirmed by a court Yes ☐ No ☐

TABLE OF CONTENTS

As used in this annual report, references to the "Company," "Takeda," "we," "us" and "our" are to Takeda Pharmaceutical Company Limited and, except as the context otherwise requires, its consolidated subsidiaries.

In this annual report, we present our audited consolidated financial statements as of March 31, 2022 and 2023 and for the fiscal years ended March 31, 2021, 2022 and 2023. Our consolidated financial statements are prepared in accordance with International Financial Reporting Standards as issued by the International Accounting Standards Board ("IFRS"). The term IFRS also includes International Accounting Standards ("IAS") and the related interpretations of the committees (Standard Interpretations Committee ("SIC") and International Financial Reporting Interpretations Committee ("IFRIC")).

As used in this annual report, "yen," "¥" or "JPY" means the lawful currency of Japan, "U.S. dollar," "$" or "USD" means the lawful currency of the United States of America ("U.S.") and "euro," "€" or "EUR" means the lawful currency of the member states of the European Monetary Union.

*As used in this annual report, "ADS" means an American Depositary Share, representing 0.5 shares of the Company's common stock, and "ADR" means an American Depositary Receipt evidencing one or more ADSs. See "*Item 12. Description of Securities Other Than Equity Securities—D. American Depositary Shares.*" "Notes" refers to the series of notes issued by us and registered under Section 12(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act") listed on the cover page of this annual report. References to "our securities" refer to collectively to our ADSs, the shares of our common stock and the notes.*

As used in this annual report, except as the context otherwise requires, the "Companies Act" means the Companies Act of Japan.

Amounts shown in this annual report have been rounded to the nearest indicated digit unless otherwise specified. In tables and graphs with rounded figures, sums may not add up due to rounding.

Special Note Regarding Forward-Looking Statements

This annual report contains forward-looking statements. These statements appear in a number of places in this annual report and include statements regarding the intent, belief, or current and future expectations of our management with respect to our business, financial condition and results of operations. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "would," "expect," "intend," "project," "plan," "aim," "seek," "target," "anticipate," "believe," "estimate," "predict," "potential" or the negative of these terms or other similar terminology. These statements are not guarantees of future performance and are subject to various risks and uncertainties. Our actual results, performance or achievements, or those of our industry, may differ materially from any future results, performance or achievements expressed or implied by these forward-looking statements. In addition, these forward-looking statements are necessarily dependent upon assumptions, estimates and data that may be incorrect or imprecise and involve known and unknown risks and uncertainties. These forward-looking statements include, among other topics, statements regarding:

- our goals and strategies;
- our ability to develop and bring to market new products, including expectations for our pipeline, our business development activities and our ability to manufacture and supply;
- expected changes in our revenue, costs, expenditures, operating income or other components of our results;
- expected changes in the pharmaceutical industry or in government policies and regulations relating to it;
- the ability to achieve the expected benefits of businesses we may acquire;
- developments regarding or the outcome of any litigation or other legal, administrative, regulatory or governmental proceedings;
- information regarding competition within our industry, including the timing of anticipated competition from generics or biosimilars of our marketed products based on the expiration of patents or regulatory exclusivity or otherwise;
- the impact of the COVID-19 pandemic;
- our ability to reduce our greenhouse gas emissions, whether via internal energy conservation measures, future advancements in renewable energy or low carbon energy technology; or
- the effect of economic, political, legislative or other developments on our business or results of operations, including changes with respect to interest rates, foreign exchange rates, inflation, third party suppliers and payers.

Forward-looking statements regarding operating income and operating results are particularly subject to a variety of assumptions, some or all of which may not be realized. Accordingly, the forward-looking statements included in this annual report should not be interpreted as predictions or representations of future events or circumstances.

Potential risks and uncertainties include those identified and discussed in "Item 3. Key Information—D. Risk Factors," "Item 4. Information on the Company," "Item 5. Operating and Financial Review and Prospects" and elsewhere in this annual report. Given these risks and uncertainties, undue reliance should not be placed on any forward-looking statements, which speak only as of the date of this annual report. Except as required by law, we disclaim any obligation to update or review any forward-looking statements contained in this annual report, whether as a result of new information, future events or otherwise.

Part I

Item 1. Identity of Directors, Senior Management and Advisers

A. Directors and Senior Management

Not applicable.

B. Advisers

Not applicable.

C. Auditors

Not applicable.

Item 2. Offer Statistics and Expected Timetable

A. Offer Statistics

Not applicable.

B. Method and Expected Timetable

Not applicable.

Item 3. Key Information

A. [Reserved]

B. Capitalization and Indebtedness

Not applicable.

C. Reasons for the Offer and Use of Proceeds

Not applicable.

D. Risk Factors

Any investment in our securities involves risk. Investors should carefully consider, in light of their own financial circumstances and investment objectives, the following risks before making an investment decision with respect to our securities. If any of the following risks actually occur, it could have a material adverse effect on our business, financial condition, results of operations, future prospects, and the market value of our securities.

The risks discussed below are those that we believe are material, but these risks and uncertainties may not be the only risks that we face. Additional risks that are not known to us at this time, or that are currently believed to be not material, could also have a material adverse effect on our business, financial condition, results of operations, future prospects and the market value of our securities.

Risks Relating to Development, Production and Marketing of Pharmaceutical Products

Research and development of pharmaceutical products are expensive and subject to significant uncertainties, and we may be unsuccessful in bringing commercially successful products to market or recouping development costs.

Our ability to offset the effects of losses of exclusivity in our existing products and to continue to grow our business depends significantly on the success of our research and development activities in identifying, developing and successfully commercializing new products in a timely and cost-effective manner. To accomplish this, we commit substantial efforts, funds and other resources to research and development, both in-house and through collaborations with third parties. However, these research and development programs are expensive and involve intensive preclinical evaluation and clinical trials in connection with a highly complex and lengthy regulatory approval process. We discuss regulatory considerations below under "—If we fail to comply with government regulations over product development, regulatory approvals and reimbursement requirements, our business could be adversely affected." The research and development process for a new biopharmaceutical product also requires us to attract and retain sufficient numbers of highly-skilled employees and can often take more than ten years from discovery to commercial launch. Even if we successfully develop and bring to market new products, there is only a limited available patent life in which to recoup these development costs.

During each stage of the approval process and post-approval life cycle of our products, there is a substantial risk that we will encounter serious obstacles, including unfavorable results or indications of safety concerns regarding a new compound; difficulty or delays in enrolling patients or in administering clinical trials; delays in completing formulation and other testing and work necessary to support an application for regulatory approval; insufficient clinical trial data to support the safety or efficacy of the product candidate; difficulties in maintaining supply chains in investigational new drugs or commercial products; failure to bring a product to market prior to a competitor, or to develop a product sufficiently differentiated from a competing product to achieve significant market share; difficulty in obtaining reimbursement at satisfactory rates for our approved products from governments and insurers; difficulty in obtaining regulatory approval for additional indications; failure to enter into or implement successful alliances for the development and/or commercialization of products or the inability to manufacture sufficient acceptable quantities of a product candidate for development or commercialization activities in a timely or cost-efficient manner. Moreover, the degree of market acceptance of any approved product candidate by the medical community, including physicians, healthcare professionals and patients, will depend on a number of factors, including changes in unmet medical need, relative convenience and ease of administration, the prevalence and severity of any adverse reactions, availability of alternative treatments, pricing and our sales and marketing strategy. Activities described above become more difficult during pandemics, such as the COVID-19 pandemic, which may result in more serious obstacles to advancing research and development activities.

In addition, to the extent that new regulations cause increases in the costs of obtaining and maintaining product authorizations or limit the economic value of a new product to its originator, our profitability and growth prospects could be diminished. Development of new and innovative products can also require the use of emerging platforms and technologies for which regulations either do not yet exist or are under development or modification. This may lead to greater uncertainty and risk in establishing the necessary data for approvals to conduct clinical trials and/or receiving marketing approvals.

As a result of the foregoing or other factors, we may decide to delay, discontinue, terminate or externalize the development of potential pipeline products in which we have invested significant resources, even where the product is in the late stages of development, and have done so in the past. For example, in 2021, we terminated Phase 2 clinical studies of TAK-994 due to the emergence of a liver-related safety signal. In June 2022, we decided not to proceed with further development of TAK-994. In addition, a Phase 3 clinical study of pevonedistat in patients with higher-risk myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML) and low-blast acute myeloid leukemia (AML) did not achieve pre-defined statistical significance for the primary endpoint of event-free survival. Following a review of these trial results, we decided to terminate our development program for pevonedistat.

There can also be no assurance that we will be successful in bringing new products to market, marketing them, achieving sufficient acceptance thereof and recouping our investments in their development. For example, our pipeline compounds may not receive regulatory approval, obtain anticipated labeling, become commercially successful or achieve satisfactory rates of reimbursement.

Additionally, products approved for use and successfully marketed in one market may be unable to obtain regulatory approval, become commercially successful or achieve satisfactory rates of reimbursement in other markets. Even following initial regulatory approval, the success of a product may be adversely affected by safety and efficacy finding in larger real-world patient populations, as well as by the market entry of competitive products or other product-related developments. For example, in March 2022, Takeda announced that it had received a Complete Response Letter (CRL) from the U.S. Food and Drug Administration (the "FDA") in response to a Prior Approval Supplement (PAS) for NATPARA (parathyroid hormone) for Injection that Takeda submitted to the FDA in late 2021. The PAS was intended to address the potential for rubber particulate formation, which was the issue that led to the U.S. recall of NATPARA in September 2019. The CRL stated that it could not be approved

in its current form. Later in 2022, amid significant ongoing supply challenges specific to the product, Takeda announced its decision to discontinue global manufacturing of NATPAR/NATPARA at the end of 2024. Additionally, Takeda announced in February 2023 that it received a notification from the Government of Japan's Ministry of Health, Labour and Welfare (the "MHLW") canceling the purchase of 141.76 million doses of COVID-19 vaccine Nuvaxovid Intramuscular Injection remaining under an agreement with the MHLW to supply 150 million doses of the vaccine.

As a result, we may be unable to earn returns on investments that we originally anticipated or at all, or may be forced to revise our research and development strategy, and our business, financial condition and results of operations could be materially and adversely affected.

If we fail to comply with government regulations over product development, regulatory approvals and reimbursement requirements, our business could be adversely affected.

Obtaining marketing approval for pharmaceutical products is a lengthy, complex and highly regulated process that requires intensive preclinical and clinical data, and the approval process can vary significantly depending on the regulatory authority. Relevant health authorities may, at the time of the filing of the application for a marketing authorization, or later during their review, impose requirements that can evolve over time, including requiring additional clinical trials, and such authorities may delay or refuse to grant approval. Even where we have obtained marketing approval for a product in one or more major markets, we may need to invest significant time and resources in applying for approval in other markets, and there is no assurance that we will be able to obtain such approval. For example, despite obtaining conditional approvals from the FDA, the United Kingdom's Medicines and Healthcare Products Regulatory Agency and China's National Medical Products Administration (the "NMPA") for EXKIVITY (mobocertinib) for the second-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, in 2022, Takeda withdrew its application for conditional approval from the European Medicines Agency (the "EMA") for such second-line treatment after initial evaluation by the agency. Health authorities are increasingly focused on product safety and on the risk/benefit profile of pharmaceutical products, which could lead to more burdensome and costly approval processes and negatively affect our ability to obtain regulatory approval for products under development. For example, the FDA, the EMA, the MHLW and the NMPA have been implementing strict requirements for approval, particularly in terms of the volume of data needed to demonstrate a product's efficacy and safety.

Even after regulatory approval is obtained, marketed products are subject to various post-marketing commitments, including continual review, risk evaluations, comparative effectiveness studies and, in some cases, requirements to conduct post-marketing clinical trials to gather additional safety and other data. Regulatory authorities in many countries have worked to enhance post-approval monitoring in recent years, which has increased post-approval regulatory burdens. Post-regulatory approval reviews and data analyses can lead to the issuance of recommendations by government agencies, specialized organizations, health professionals or patients regarding the use of products. For example, such recommendations could include a request to limit the patient population of a drug's indication, the imposition of marketing restrictions, including changes in package insert or labeling, or the suspension or withdrawal of the product. Any such recommendation, whether implemented or not, could result in reductions in sales volume and/or new or increased concerns about the adverse reactions or efficacy of a product. These substantial regulatory requirements have, over time, increased the costs associated with maintaining regulatory approvals and achieving reimbursement for our products.

If the regulatory approval process or post-approval, reimbursement, monitoring or other requirements become significantly more burdensome in any of our major markets, we could become subject to increased costs and may be unable to obtain or maintain approval to market our products. Any such adverse changes could materially and adversely affect our business, results of operations or financial condition.

If we fail to comply with laws and regulations governing the sales and marketing of our products, our business could be adversely affected.

We engage in various marketing, promotional and educational activities pertaining to, as well as the sale of, pharmaceutical products in a number of jurisdictions around the world. The promotion, marketing and sale of pharmaceutical products and medical devices is highly regulated and the sales and marketing practices of market participants have been subject to increasing supervision by governmental authorities, and we believe that this trend will continue.

In the U.S., our sales and marketing activities are monitored by several regulatory authorities and law enforcement agencies, including the FDA, the U.S. Department of Health and Human Services (the "HHS"), the U.S. Department of Justice, the Drug Enforcement Administration (the "DEA") and the U.S. Securities and Exchange Commission (the "SEC"). In addition, our use of data, including sensitive patient information, and of technology, including machine learning and artificial intelligence, is regulated by the Federal Trade Commission as well as various states under evolving standards. These authorities and agencies and their equivalents in other countries have broad authority to investigate market participants for potential violations of laws relating to the sale, marketing and promotion of pharmaceutical products and medical devices, including the False Claims Act, the Anti-Kickback Statute, the United Kingdom Bribery Act of 2010 and the Foreign Corrupt Practices Act, among others, for alleged improper conduct, including corrupt payments to government officials, improper payments to medical professionals, off-label marketing of pharmaceutical products and medical devices, the submission of false claims for reimbursement by the federal government and the use or misuse of data and technology. Healthcare companies may also be subject to enforcement actions or prosecution for such improper conduct. Any inquiries or investigations into our operations, or enforcement or other regulatory action against us, by such authorities could result in significant defense costs, fines, penalties and injunctive or administrative remedies, distract management to the detriment of the business, result in the exclusion of certain products, or us as a whole, from government reimbursement programs or subject us to regulatory controls or government monitoring of its activities in the future. We are also subject to certain ongoing investigations by governmental agencies.

Government policies and other pressures to reduce medical costs could have an adverse effect on sales of our pharmaceutical products.

We are subject to governmental regulations mandating price controls in various countries in which we operate. The growth of overall healthcare costs as a percentage of gross domestic product in many countries means that governments and consumers are under intense pressure to control spending even more tightly. See Item 4. Information on the Company—B. Business Overview-Third Party Reimbursement and Pricing.

In the U.S., managed care groups, as well as institutional and governmental purchasers, have put increased pricing pressure on drug manufacturers. In particular, as managed care groups have grown in size due to market consolidation, pharmaceutical companies have faced increased pressure in pricing and usage negotiations and are engaged in fierce competition to have their products included in the care providers' formularies. Moreover, as a result of the legislative and regulatory environment, in the U.S. we continue to experience heightened pricing pressure on, and limitations on access to, our branded pharmaceutical products sold in the U.S. In 2022, Congress passed the Inflation Reduction Act (the "IRA"), which significantly changes the compensation terms for drugs under the Medicare program, including by imposing penalties on manufacturers who raise drug prices faster than inflation, instituting a cap on out-of-pocket expenditures by Medicare beneficiaries and allowing the federal government to set prices for certain drugs covered under Medicare beginning in 2026. We expect the IRA to negatively impact sales and profits and may lead to further political pressure or legislative, regulatory or other efforts to introduce lower prices, reduce spending on the Medicare and Medicaid programs, expand and strengthen the Affordable Care Act, and lower the overall spending by the government on prescription medicines. As a result, we expect the health care industry in the U.S. will continue to be subject to increased pricing and spending pressure.

In Japan, manufacturers of pharmaceutical products must have new products listed on the National Health Insurance (the "NHI") Drug Price Standard, a price list published by the MHLW (the "NHI price list"). The NHI price list provides rates for calculating the price of pharmaceutical products used in medical services provided under various public medical care insurance systems. Prices on the NHI price list have been previously subject to revisions based on the actual prices and amounts by which the pharmaceutical products are purchased by medical institutions in Japan, and the average price of previously listed products generally decreases as a result of these price revisions. The Japanese government is currently undertaking healthcare reform initiatives with the goal of sustaining the universal coverage of the NHI program. As part of these initiatives, the annual NHI price list revision was introduced in April 2021, which could lead to more frequent downward price revisions. The government is also addressing the efficient use of drugs, including the further promotion of generic use that slightly fell short of a target of 80% penetration by volume by September 2020 with respect to products for which market exclusivity has expired. In addition, products on the NHI price list nominated based on pre-defined criteria, such as innovativeness and the financial impact, are subject to a cost-effectiveness evaluation under MHLW rules, and subject to price adjustments depending on the outcome of this evaluation.

In Europe, drug prices have been subject to downward pressure due to measures implemented in each country to control drug costs, and prices continue to come under pressure due to parallel imports, generic competition, increasing use of health technology assessment based upon cost-effectiveness and other factors. European pricing and reimbursement authorities have also intensified efforts to increase transparency of prices as well as exchange of information among the various European pricing authorities in order to raise pressure towards the industry. This pricing debate has impacted the overall political climate in Europe and has triggered a European policy initiative to review the pharmaceutical industry's intellectual property incentives with a particular emphasis on orphan drugs. While we expect that any new legislation in this area would take at least two to three years to be adopted, it could have significant impact on our business model.

We are also facing similar pricing pressures in other regions, such as various emerging countries including China. We expect such pricing pressures to continue as we expand our business in those regions and countries.

We expect these efforts to control costs to continue as healthcare payers around the globe, in particular government-controlled health authorities, publicly funded or subsidized health programs, insurance companies and managed care organizations, increasingly pursue initiatives to reduce the overall cost of healthcare, restrict access to higher-priced new medicines, increase the use of generics and impose overall price revisions. Such further implementation of these policies could have a material adverse effect on our business, financial condition and results of operations.

The expiration or loss of patent or regulatory data or marketing protection over our products or patent infringement by generic or biosimilar manufacturers could lead to significant competition from generic versions or biosimilars of the relevant product and/or lead to declines in market share and price levels of our products.

Our pharmaceutical products are generally protected for a defined period per jurisdiction by various patents (including those covering drug substance, drug product, approved indications, methods of administration, methods of manufacturing, formulations and dosages) and/or regulatory exclusivity, which are intended to provide us with exclusive rights to market the products for the life of the patent or duration of the regulatory data protection period. The loss of regulatory exclusivity for pharmaceutical products may open such products to competition from generic substitutes that are typically priced significantly lower than the original products, which typically adversely affects the market share and prices of the original products.

Generic or biosimilar substitutes have high market shares in a number of key markets, including the U.S., Europe, Japan and many emerging countries, and the adverse effects of the launch of generic products are particularly significant in such markets. The introduction of generic or biosimilar versions of a pharmaceutical product typically leads to a swift and substantial decline in the sales of the original product. Our continued innovation efforts cannot fully mitigate the impact of competition from generics or biosimilars. In the U.S., the European Union ("EU") and Japan for example, political pressure to reduce spending on prescription drugs has led to legislation and other measures that encourage the use of generic products. In Japan, the government is implementing various measures to control drug costs, including by encouraging medical practitioners to use and prescribe generic drugs, and in April 2021 announced its intention to raise generic drug penetration with respect to products for which market exclusivity has expired, to 80% by volume in all prefectures (regions) by the end of the fiscal year ending March 31, 2023. Legislation has also been passed in the U.S. and Europe encouraging the use of biosimilar products. Similar to generics, biosimilars aim to provide less expensive versions of

innovative biologic products. Legislation has provided abbreviated pathways for the approval and marketing of biosimilar products, which may affect the profitability and commercial viability of our biologic products.

Certain products of ours have begun, or are expected over the next several years, to face declining sales due to the loss of patent protection or regulatory exclusivity. For example, following the expiration of patent protection covering the formulation of VELCADE and pediatric regulatory exclusivity, generic bortezomib products entered the market in 2022. Patent protection covering VYVANSE and the associated pediatric regulatory exclusivity are scheduled to expire in the U.S. in August 2023, which we anticipate will lead to declines in sales. Furthermore, our current top selling product, ENTYVIO, will face loss of regulatory exclusivity in the latter half of this decade and certain patents covering various aspects of this product are expected to expire in 2032. See “Item 4. Information on the Company—B. Business Overview—Intellectual Property” for details.

We may also be subject to competition from generic or biosimilar drug manufacturers prior to the expiration of patents if a manufacturer successfully challenges the validity of our patents, if a manufacturer is able to design around our patents, or if a manufacturer obtains approval of their product and launches it at risk (i.e. prior to a judicial determination). If such a launch occurred prior to completion of court proceedings, a court may decline to grant a preliminary injunction. While we may be entitled to obtain damages subsequently, the amount we may ultimately be awarded and able to collect may be insufficient to compensate for the loss of sales and other harm caused to us. Furthermore, if we lose patent protection as a result of an adverse court decision or a settlement, in certain jurisdictions, we may face the risk that government and private third-party payers and purchasers of pharmaceutical products may claim damages alleging they have over-reimbursed or overpaid for a drug.

If our patent and other intellectual property rights are infringed by generic or biosimilar drug manufacturers or other third parties, we may not be able to take full advantage of the potential or existing demand for our products. The protection that we are able to obtain for our prescription drugs varies from product to product and country to country and may not always be sufficient because of local variations in issued patents, or differences in national law or legal systems, including inconsistency in the enforcement or application of law and limitations on the availability of meaningful legal remedies. In particular, patent protection in emerging markets is often less certain than in developed markets. Certain countries may also engage in compulsory licensing of pharmaceutical intellectual property to other manufacturers as a result of local political pressure. Furthermore, the attention of our management and other personnel could be diverted from their normal business activities if we decide to litigate against such infringement. The realization of any such risks could adversely and materially affect our business, financial condition and results of operations.

We may have difficulty maintaining the competitiveness of our products.

The pharmaceutical industry is highly competitive, and in order to maintain the competitiveness of our product portfolio, we are required to maintain ongoing, extensive research for technological innovations, including new compounds, to develop and commercialize existing pipeline products, to expand our product portfolio through acquisitions, partnerships and in-licensing, and to market our products effectively, including by communicating the efficacy, safety and value of our products to healthcare professionals. However, healthcare professionals and consumers may choose competitors’ products over ours, if they perceive these products to be safer, more reliable, more effective, easier to administer or less expensive. The success of any product depends on our ability to effectively communicate with and educate healthcare professionals and patients and convince them of the advantage of our products over those of our competitors. We often carry out costly clinical trials even after our products have been launched to produce data to be utilized for these purposes, but such trials do not always produce the desired outcomes. Certain competitors have greater financial and other resources to conduct such trials in more detail and with larger patient populations, which may ultimately enable them to promote their products more effectively than we do. Furthermore, if relevant regulators increase their approvals of new therapies developed by competitors for the conditions treated by our products, such as in order to increase the number of treatment options available for rare or orphan diseases, our business and results of operations could be materially and adversely affected.

In recent years, competitors have introduced novel hemophilia products, or such products have been approved for additional uses, which may affect (and in certain cases has affected) sales of our recombinant and plasma-based hemophilia products, such as our factor FVIII products and anti-inhibitor coagulant complex product. Certain competitors are developing other hemophilia therapies, including gene-based therapies, and in 2022, the FDA approved the first gene therapy for hemophilia B. These developments could also affect sales of our recombinant and plasma-based therapies. Increased competition from new products or therapies could similarly affect our other products.

In Japan, the steady introduction of drugs already marketed outside Japan by overseas competitors has led to increased competition. In addition, new competing products or the development of superior medical technologies and other treatment options could make our products or technologies lose their competitiveness or become obsolete. As discussed above, our products are also subject to competition from inexpensive generic versions or biosimilars of our products, as well as those of our competitors’ products, upon the expiration or loss of related patent protection and regulatory data protection, which may result in loss of market share. If we are unable to maintain the competitiveness of our products, our business, financial position and results of operations could be materially and adversely affected.

Furthermore, sales of the rare disease portfolio are particularly concentrated among small groups of customers, and we may be disproportionately affected by changes in their purchasing patterns, including if we are unable to maintain the competitiveness of our products.

We may not be able to adequately expand our product portfolio through third-party alliance arrangements.

We expect that we will continue to collaborate with third parties for key aspects of our business, including the discovery and development of new products, in-licensing products, and the marketing and distribution of approved products. A major part of our research and development strategy is to initiate alliances with third parties in the biotechnology industry, academia and the public sector, and we believe that the overall strength of our research and development program and product pipeline depends on our ability to identify and initiate partnerships, in-licensing arrangements and other collaborations with third parties. However, there can be no assurance that any of our third-party alliances will lead to the successful development and marketing of new products. Moreover, reliance on third-party alliances subjects us to a number of risks, including:

- We may be unable to identify suitable opportunities at a reasonable cost and on terms that are acceptable to us due to active and

intense competition among pharmaceutical groups for alliance opportunities or other factors;

- Entering into in-licensing or partnership agreements may require the payment of significant upfront and/or milestones payments well before the relevant products are placed in the market, without any assurance that such investments will ultimately become profitable in the long term. To the extent such payments are recorded as assets on our consolidated statement of financial position, any termination of the relevant partnership could require us to recognize an impairment loss up to the full value of such assets;
- When we research and market our products through collaboration arrangements, the performance of certain key tasks or functions are the responsibility of our collaboration partners, who may not perform effectively or otherwise meet our expectations; and
- Decisions may be under the control of or subject to the approval of our collaboration partners, and we may have differing views or be unable to agree upon an appropriate course of action. Any conflicts or difficulties that we may have with our partners during the course of these agreements or at the time of their renewal or renegotiation or any disruption in the relationships with our partners may affect the development, launch and/or marketing of certain of our products or product candidates.

In addition, a licensor or partner may attempt to terminate its license or partnership agreement with us or elect not to renew it to pursue other marketing opportunities. Our licensors or partners also could merge with or be acquired by another company or experience financial or other setbacks unrelated to our alliance arrangements. Any of these events may force us to terminate a development project and adversely affect our ability to adequately expand or maintain our product portfolio.

Our use of third parties for the performance of certain key business functions, particularly product manufacture and commercialization, heightens the risks faced by our business.

We commonly use suppliers, vendors and partners, including alliances with other pharmaceutical companies, for certain key aspects of our business, including manufacturing and commercialization of products, support for information technology systems and certain human resource functions. We do not control these partners, but we depend on them in ways that may be significant to us. If these parties fail to meet our expectations or fulfill their obligations to us, we may fail to receive the expected benefits. In addition, if any of these third parties fails to comply with applicable laws and regulations in the course of its performance of services for us, there is a risk that we may be held responsible for such violations as well. This risk is particularly serious in emerging markets, where corruption is often prevalent and where many of the third parties on which we rely do not have internal compliance resources comparable to our own. Any such failures by third parties, in emerging markets or elsewhere, could adversely affect our business, reputation, financial condition or results of operations. Moreover, global supply chains have been affected by such varying but interconnected factors as the COVID-19 pandemic, the Russian invasion of Ukraine and resulting disruptions to logistics, transportation, energy and other industries and significantly increased inflation in a number of markets. These pressures on global supply chains may also harm the ability of our third-party partners to supply us with the products and services we need to administer our business.

Our dependence on third parties for the inputs for our products subjects us to various risks, and changes in the costs of materials may adversely affect our profitability.

Although we develop and manufacture the active ingredients used in some of our products at our own facilities, we are dependent on third-party suppliers for a substantial portion of the raw materials and compounds used in the products we produce. The price and availability of the raw materials for our products, including chemical compounds and biologics, are subject to the effects of weather, natural disasters, market forces, the economic environment, pandemics (such as the recent COVID-19 pandemic), geopolitical events, fuel costs and foreign exchange rates. If our cost for such materials increases, we may not be able to make corresponding increases in the prices of our products due to regulations, market conditions or our relationships with our customers, and as a result, our profitability could be materially and adversely affected.

In particular, we rely on third-party suppliers of key manufacturing inputs of certain drug products. Furthermore, certain active ingredients for these products are sourced from a single supplier. We also rely in part on third-party sources to provide the donated plasma necessary for our plasma-derived therapies. In addition, although we often dual-source certain key products and/or active ingredients, we currently rely on a single source for production of certain key products, and/or active ingredients and final drug products. Sources of some materials may be limited to a single supplier, and if such a supplier faces any difficulty in supplying the materials, we may not be able to find an alternative supplier in a timely manner or at all. If materials become unavailable or if quality problems related to the materials arise, we may be forced to halt production and sales of products that use them. In the event that any of our third-party suppliers is delayed in its delivery of such raw materials or compounds, is unable to deliver the full quantity ordered by us at the appropriate level of quality, or is unable to deliver any raw materials or compounds at all, our ability to sell our products in the quantities demanded by the market may be impaired, which could damage our reputation and relationships with customers and patients. In such a case, our business and results of operations could be adversely affected.

The manufacture of our products is technically complex and highly regulated, and supply interruptions, product recalls or other production problems caused by unforeseen events may reduce sales, adversely affect our operating results and financial condition and delay the launch of new products.

The manufacture of our products (from active pharmaceutical ingredients through to finished products) is technically complex and highly regulated, and as a result we may experience difficulties or delays including but not limited to seizure or recalls of products or shut-downs of manufacturing plants; problems with business continuity, including as a result of a natural or man-made disaster, at one of our facilities or at a critical supplier or vendor; failure by us or by any of our vendors or suppliers to comply with the Good Manufacturing/Laboratory Practice (the “GMP/GLP”) and other applicable regulations and quality assurance guidelines, which could lead to manufacturing shutdowns, product shortages, delays in product manufacturing and /or administrative, enforcement or other actions by regulatory authorities if regulatory authorities deem our products to be non-compliant with or otherwise in violation of applicable laws; problems with manufacturing, quality assurance/quality control, storage or supply,

or governmental approval delays, due to our consolidation and rationalization of manufacturing facilities and the sale or closure of certain sites; failure of a sole source or single source supplier to provide us with necessary raw materials, supplies or finished goods for an extended period of time, which could impact continuous supply; failure of a third-party manufacturer to supply us with semi-finished or finished products on time; construction or regulatory approval delays related to new facilities or the expansion of existing facilities; the inability to obtain sufficient components or raw materials on a timely basis or at a cost-effective price due to public health crises, medical epidemics or pandemics such as the COVID-19 pandemic; additional costs related to deficiencies identified by regulatory agencies in connection with inspections of our facilities, and enforcement, remedial or punitive actions by regulatory authorities if we fail to remedy any deficiencies; and other manufacturing or distribution problems, including limits to manufacturing capacity due to regulatory requirements (e.g. Registration, Evaluation, Authorisation and Restriction of Chemicals ("REACH") regulation in the EU), changes in the types of products produced, physical limitations or other business interruptions, that could impact continuous supply. For example, in 2019, we issued a recall in the United States of NATPARA (parathyroid hormone) due to the potential for rubber particulate formation and, in 2022, the FDA issued a CRL in response to our Prior Approval Supplement (PAS) with respect to NATPARA (parathyroid hormone) to address this potential issue and indicated that it could not approve the PAS in its current form. In late 2022, Takeda made its decision that it would discontinue manufacturing NATPARA for injection globally at the end of 2024 due to unresolved supply issues that are specific to the product.

In addition, despite efforts at compliance, from time to time we or our partners may receive notices of manufacturing, quality-related, or other observations following inspections by regulatory authorities around the world, as well as official agency correspondence regarding compliance. For example, on June 9, 2020 the FDA issued a warning letter related to our manufacturing plant in Hikari, Yamaguchi, Japan which included several technical observations, including observations about procedures, personnel, records, investigations, training, equipment, and oversight. Based on our responses and corrective actions, the FDA revised the inspection classification to Voluntary Action Indicated and determined that the conditions in the Warning Letter were addressed and, as a result, the Waring Letter was closed. The corrective actions resulted in a temporary supply shortage of Leuprorelin, a product which we supply to AbbVie, Inc. ("AbbVie") pursuant to a supply agreement. AbbVie has since filed a lawsuit against us on November 6, 2020 specifying an alleged breach of contract. We or our partners may receive additional or similar observations, correspondence and claims in the future, whether regarding the Hikari plant or otherwise. If we are unable to resolve these observations and address regulator concerns and claims from partners in a timely fashion, our business, financial condition and results of operations could be materially affected. See "*—We are involved in litigation relating to our operations on an ongoing basis, and such litigation could result in financial losses or harm our business"* for further discussion on risks associated with litigation and lawsuits relating to our operations.

The development and manufacture of biologics and cell therapies present heightened or additional risks. The manufacture of biologics, including cell therapy products, is highly complex and is characterized by inherent risks and challenges, such as raw material inconsistencies, logistical and sourcing challenges, significant quality control and assurance requirements, manufacturing complexity (including heightened regulatory requirements), short shelf life and significant manual processing. Unlike products that rely on chemicals for efficacy, such as most pharmaceuticals, biologics are more complex to characterize due to the inherent variability of biological input materials. As a result, assays of the finished product may not be sufficient to ensure that the product will perform in the intended manner. Problems with the manufacturing process, even minor deviations from the normal process, could result in product defects or manufacturing failures that result in, among other things, lot failures, product recalls, product liability claims or insufficient inventory, which could be costly to us or result in reputational damage.

Furthermore, sourcing and transportation of plasma and production and distribution of plasma-derived products is complex, capital intensive and subject to extensive regulation. Efforts to increase the collection of plasma may require strengthening acquisition and third-party contracting capacities and successful regulatory approval of additional plasma collection facilities and plasma fractionation facilitates. Further development of such capacities and facilities involves a lengthy regulatory process and is highly capital intensive. In addition, access to and transport and use of plasma may be subject to restrictions by governmental agencies. If we are unable to manage these inherent risks and challenges, we may lose market share or customer confidence, be required to record charges related to idle capacity or impairment on facilities or take other actions which could materially and adversely affect the Plasma-Derived Therapies business.

Any of the above may reduce sales, delay the launch of new products, and adversely affect our business, financial condition and results of operations.

The illegal distribution and sale by third parties of counterfeit versions of our products or products stolen from us could have an adverse effect on our reputation and business.

Third parties may illegally distribute and sell counterfeit versions of our products, which do not meet the rigorous manufacturing and testing standards to which our products are subject. A patient who receives a counterfeit drug may be at risk for a number of dangerous health consequences. Reports of adverse reactions to counterfeit drugs or increased levels of counterfeiting could materially affect patient confidence in our products, which could have a material adverse effect on our reputation and financial results. In addition, thefts at warehouses, at plants, or in transit of inventory that is not properly stored or that is sold through unauthorized channels could materially and adversely affect patient safety, our reputation and our results of operations.

Risks Relating to Our Business Strategies

We have substantial debt which may limit our ability to execute our business strategy, refinance existing debt or incur new debt, and if we are unable to maintain sufficient financial strength, we could be at a greater risk of a downgrade of our credit ratings.

Our consolidated bonds and loans were 4,382.3 billion JPY as of March 31, 2023, the majority of which was incurred in connection with the acquisition of the entire issued and to-be-issued share capital of Shire pursuant to a Scheme of Arrangement under the laws of Jersey (the "Shire Acquisition") or represents the related indebtedness of Shire that is included in our consolidated statements of financial position. This significant amount of aggregate debt and the substantial amount of cash required for payments of interest and principal could adversely affect our liquidity. We are also required to comply with certain covenants within various financing arrangements and violations of such covenants may require the acceleration and immediate repayment of the indebtedness, which may in turn have a material adverse effect on our financial condition, cash flows, business and results of operations. Furthermore, we may desire to or be required from time to time to incur additional borrowings, including in relation to the repayment or refinancing of any of our currently outstanding indebtedness. Our ability to arrange new financing, or a re-financing and the terms thereof will depend on our financial position and performance, prevailing market conditions (including fluctuations in market interest rates, which have increased significantly in the U.S. and, to a lesser extent, other jurisdictions in the fiscal year ended March 31, 2023) and other factors beyond our control. Moreover, if we decide to refinance indebtedness as it comes due, our overall leverage may not necessarily decrease.

Credit rating agencies routinely evaluate our business, and their ratings are based on a number of factors, including our leverage, ability to generate cash flows, overall financial strength and diversification, as well as other factors beyond our control, such as the state of the global economy and our industry generally. While our credit ratings remain investment grade, each rating agency reviews its ratings periodically, and there is no assurance that the current credit ratings assigned to us will not be downgraded. A downgrade of our credit rating may materially and adversely affect the market prices of our equity and debt securities, including the notes, the interest rates at which our borrowings and debt securities are issued, and fees charged to us by current or future lenders. This could make it significantly more costly for us to borrow money, to issue debt securities and to raise certain other types of capital and/or complete additional financings. Such negative credit rating actions and the underlying reasons for such actions could materially and adversely affect our cash flows, results of operations and financial condition and the market price of, and our ability to pay the principal and interest on our debt securities.

We face risks from the pursuit of acquisitions, and the anticipated benefits and synergies resulting from acquisitions may not be realized.

We regularly pursue acquisitions for several reasons, including strengthening our pipeline, complementing existing lines of business, adding research and development capabilities or pursuing other synergies. The pursuit of these acquisitions requires the commitment of significant management and capital resources in various stages, from the exploration of potential acquisition targets to the negotiation and execution of an acquisition to the integration of an acquired business into our own. The required commitment of time and resources may divert the attention of management or capital or other resources away from our day-to-day business. Moreover, we may not be able to recoup the investment of capital or other resources through the successful integration of acquired businesses, including the realization of any expected cost or other synergies. Specifically, we may encounter the following difficulties: we may face significant challenges in combining the infrastructure, management and information systems of acquired companies with ours, including integrating research and development, manufacturing, distribution, marketing and promotion activities and information technology systems; there may be difficulties in conforming standards, controls, procedures and accounting and other policies, as well as business cultures and compensation structures; we may not be able to retain key personnel at acquired companies, or our own employees may be motivated to leave due to acquisitions; we may not be successful in identifying and eliminating redundancies and achieving other cost savings as expected; and we may not be able to successfully realize benefits from acquired products, including pipeline products under development. For example, on February 8, 2023, we acquired all of the capital stock of Nimbus Lakshmi, Inc., a wholly owned subsidiary of Nimbus Therapeutics, LLC, that owns or controls the intellectual property rights and other associated assets related to TAK-279, the allosteric TYK2 inhibitor known internally at Nimbus as "NDI-034858". While we seek to develop this molecule into an important part of our product portfolio, this remains subject to ongoing development, and we may be unable to develop it into a marketed product as successfully as expected or at all, which could harm our ability to recoup our investment in the acquisition, require us to record impairment charges for related intangible assets or otherwise adversely affect our business, results of operations or financial condition.

Integrating the operations of multiple new businesses with that of our own is a complex process that requires significant management attention and resources. The integration process may disrupt our existing and other newly acquired businesses and, if implemented ineffectively, could have an adverse impact not only on our ability to realize the benefits of a given acquisition but also on the results of our existing operations. Integration-related risks may be heightened in cases where acquired businesses' operations, employees or customers are located outside our major markets and we incur higher costs than anticipated due to regulatory changes, environmental factors or foreign exchange fluctuations. We continue to pursue strategic business acquisitions globally as a key part of our continuous growth strategy. If we are not able to achieve the anticipated benefits of any future acquisitions in full or in a timely manner, we could be required to recognize impairment losses, we may not be able to recoup our investment, and our business, financial position and results of operations could be materially and adversely affected. Particularly, we may be unable to achieve the expected revenues pursuant to licensing, co-promotion or co-development agreements or collaborations. We may also assume unexpected contingent or other liabilities, or be required to mark up the fair value of liabilities (or mark down the fair value of assets) acquired upon the close of an acquisition.

We have significant operations across the world, including emerging markets, and continued expansion into new and developing markets is a key strategy, which expose us to additional risks.

Our global operations, which encompass approximately 80 countries and regions across the world, are subject to a number of risks, including difficulties in monitoring and coordinating research and development, marketing, supply-chain and other operations in a large number of jurisdictions; risks related to laws, regulations and policies, including those implemented following changes in political leadership and trade, capital and exchange controls; changes with respect to taxation, including impositions or increases of withholding and other taxes on remittances and other payments by our overseas subsidiaries; varying standards and practices in the legal, regulatory and business cultures in which we operate, including potential inability to enforce contracts or intellectual property rights; trade restrictions and changes in tariffs; complex sanctions regimes in various countries such as the U.S., the EU and other jurisdictions, violations of which could lead to fines or other penalties; risks related to geopolitical and local political instability and uncertain business environments; changes in global, regional or local economies, or the overall political, economic or social climate, including inter-country relationships in Asia and elsewhere; acts of terrorism, war, global climate change, extreme weather events, medical epidemics or pandemics such as the recent COVID-19 pandemic, and other sources of social disruption; and difficulties associated with managing local personnel and preventing misconduct by local third-party alliance partners.

Any one or more of these or other factors could increase our costs, reduce our revenues, or disrupt our operations, with possible material adverse effects on our business, financial condition and results of operations. Further expansion overseas has been one of our key strategies, and, in the fiscal year ended March 31, 2023, regions outside of Japan accounted for 87.3% of our consolidated revenue, with the U.S. in particular contributing 52.2% of consolidated revenue. We expect that markets outside Japan, particularly the U.S. and also Europe and Canada, will continue to be increasingly important to our business and results of operations, increasing the likelihood that any of these risks is realized. We have also been taking steps to grow our business in most emerging markets, which we define to include Latin America, Asia (excluding Japan), Russia/ Commonwealth of Independent States (“CIS”) and Other (including the Middle East, Oceania and Africa). Our revenue from emerging markets was 569.0 billion JPY (or 14.1% of our total revenue) for the fiscal year ended March 31, 2023, and we intend to pursue further growth in such emerging markets. In particular, we believe that there is an attractive opportunity to grow our business in China.

However, there is no guarantee that our efforts to expand sales in emerging markets will succeed. Some countries may be especially vulnerable to periods of global financial instability or may have very limited resources to spend on healthcare. Emerging markets present particular challenges in obtaining funding, achieving market access for our products and successfully ensuring that we receive appropriate levels of reimbursement. Emerging markets also tend to require substantial efforts in patient support and other programs. All of these factors may adversely affect the profitability of our businesses in these emerging markets.

In response to the Russian invasion of Ukraine begun in February 2022, Takeda has taken action to discontinue activities in Russia that are not essential to maintaining the supply of medicines to patients and providing ongoing support to our employees, subject to compliance with all international sanctions imposed on Russia. This includes suspending all new investments, suspending advertising and promotion, not initiating new clinical trials and stopping enrollment of new patients in ongoing clinical trials. In the fiscal year ended March 31, 2023, revenue attributable to Russia/CIS represented 2.2% of our total consolidated revenue, and we did not experience a material impact from the invasion, international responses thereto or our discontinuation of non-essential activities in Russia. Depending on the future status of the crisis, however, our results of operations and financial condition, and our strategy to increase our business in the region, could be adversely affected. Among other matters, certain clinical trials may be delayed, and we may incur additional costs to find alternative locations in which to hold such trials. For example, due in part to the effects of the invasion of Ukraine on our ability to conduct clinical trials, as well as other factors such as COVID-19-related lockdowns in China, in 2022, we have announced delays in our target approval filing dates for soticlestat and for EXKIVITY for treatment of newly diagnosed non-small cell lung cancer.

In order to successfully implement our emerging markets strategy, we must also attract and retain qualified personnel, despite the possibility that some emerging markets may have a relatively limited number of persons with the required skills and training. We may also be required to increase our reliance on third-party agents within less-developed markets, which may put us at increased risk of liability. In addition, many emerging markets have currencies that fluctuate substantially, and if such currencies are devalued and we cannot offset the devaluations, our financial performance in such countries may be adversely affected. Further, many emerging markets have relatively weak intellectual property protection and inadequate protection against crime, including counterfeiting, corruption and fraud. Operations in certain emerging countries, where corruption may be more prevalent than in more developed countries and where internal compliance practices may not be well established, may also pose challenges from a legal and regulatory compliance perspective. Moreover, we may face additional legal and regulatory barriers to achieving growth, such as restrictions on the import of raw materials or other trade regulations (for example, on the import of plasma and plasma products into China) that will require us to expend additional resources to achieve our goals.

For reasons including but not limited to the above, significant parts of our operations across the world including emerging markets presents significant risks, and the realization of such risks could have a material adverse effect on our business, financial condition and results of operations.

We may experience difficulty implementing corporate sustainability-related measures, particularly those relating to the environment, or in meeting the expectations of stakeholders.

Governmental and regulatory authorities, counterparties such as vendors and suppliers, investors, the public at large and others have increasingly focused on sustainability and social responsibility-related issues, particularly as they relate to the environment. In response, we have established a company-wide environmental sustainability program as a part of Takeda’s corporate initiatives. As part of our Planet imperative, we have committed to reducing our carbon footprint, minimizing waste sent to landfill from our operations, enhancing our water stewardship practices, and engaging with our vendors and suppliers to encourage them to cooperate with these initiatives. We have also committed to achieve net-zero (as defined in the Science Based Targets initiative (SBTi) Corporate Net-Zero Standard) in greenhouse gas (GHG) emissions related to our operations (Scope 1 and Scope 2) before 2035 and for our entire value chain (including currently estimated Scope 3 GHG emissions) by 2040. However, we

may be unable to meet this commitment given the significant technological and organizational changes required. Additionally, a lack of transparency into, and a difficulty measuring, actual Scope 3 emissions remain an important challenge to overcome as part of these efforts, and we may not be successful in doing so. Moreover, although we have not yet recorded material expenses in connection with our carbon neutrality initiatives, the costs of successfully implementing them, such as the costs of carbon offsets or seeking renewable sources of energy, are currently unclear, will depend on factors outside of our control (such as the effect of governmental and societal efforts to increase the availability of carbon neutral and/or renewable energy sources and technology) and may become significant in the future. Also, these initiatives may for example require us to seek alternative vendors or suppliers or impair our ability to procure or use certain materials. To the extent that we are unable to meet the expectations of stakeholders, including governmental and regulatory authorities, counterparties, investors, or the public, our reputation may be harmed, we may face increased compliance or other costs and demand for securities issued by us and our ability to participate in the debt and equity markets may decrease. Furthermore, such standards and expectations are subject to ongoing change and refinement, and may shift in unexpected and potentially significant ways, which we may struggle to accommodate.

Our digital transformation initiatives may be unsuccessful, and our profitability may be hurt or our business otherwise might be adversely affected.

We have made and plan to continue to make significant investments in digital transformation initiatives, with the goal of modernizing our platforms, accelerating data services, enhancing our ability to innovate and equipping our employees with new skills and ways of working. These types of activities are complex and are dependent on a number of factors, including entering into successful partnerships and alliances with technology companies, as well as developing and deploying technology architecture successfully. If we do not successfully manage our digitalization initiatives, or any other related activities that we may take in the future, any expected efficiencies and benefits might be delayed or not realized, and our operations and business could be disrupted. If we fail to adequately integrate digitalization into our business, we may lose customers and market share. Even if our efforts are successful, our competitors, including established competitors or new entrants with specialized expertise, may be better able to achieve digitalization and realize its benefits, giving them a competitive advantage over us, displace any technology that we may develop or implement or make it obsolete. In addition, the costs associated with implementing these initiatives might exceed expectations, which could result in additional future charges, and we may be exposed to increased cybersecurity or related risks. The occurrence of any of these risks could have a material adverse effect on our business, financial position and results of operations.

We are increasingly dependent on information technology systems and our systems and infrastructure face the risk of theft, exposure, tampering or other intrusions.

A variety of important processes relating to the research and development, production and sale of our products depend heavily on our information systems, including cloud-based computing, or those of third party providers to whom we outsource certain business functions, including the storage and transfer of critical, confidential, sensitive or personal information regarding our patients, clinical trial subjects, vendors, customers, employees and others. We also increasingly seek to develop and collaborate on technology-based digital health products, such as mobile applications that aim to improve patient welfare in a variety of ways, which could lead us to store and transfer personal information about individual patients, customers and others. The size, age and complexity of our information technology systems make them potentially vulnerable to service interruptions, malicious intrusions and random attacks. Cyber-attacks are increasing in frequency, sophistication and intensity, and opportunistically in response to, for example, the implementation of remote working arrangements as a result of the COVID-19 pandemic. These and other cyber-attacks are made by groups and individuals with a wide range of motives (including, but not limited to, industrial espionage) and expertise, including organized criminal groups, hacktivists, nation-states and others. Cyber-attacks could include the deployment of harmful malware, denial of service attacks, worms, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. The development and maintenance of systems to safeguard against such attacks is costly and requires ongoing monitoring and updating as technologies change and efforts to overcome security measures become increasingly more sophisticated. Moreover, the costs related to these security measures are expected to continue to increase. Despite our efforts, the possibility of a future data compromise cannot be eliminated entirely, and risks associated with intrusion, exposure, tampering, and theft remain. For zero-day threats, or new vectors of attack which are currently unknown, the risk that our defenses will be inadequate are particularly pronounced.

Although we have not, to date, detected any material breaches of our information technology systems, data systems or personal information, the risk of such breaches remains and cannot be completely negated. If our data systems are compromised, our business operations may be impaired, we may lose profitable opportunities, or the value of those opportunities may be diminished, and we may lose revenue because of unlicensed use of our intellectual property or confidential or proprietary information. Cyber-attacks could significantly impact the availability of data systems that are essential to conducting routine business operations across the company, including product manufacturing or clinical development, and the recovery efforts could be both time consuming and costly. If personal information of our customers, employees or the patients we serve is misappropriated, our reputation with our customers, employees and patients may be injured resulting in loss of business and/or morale, and we may incur costs to remediate possible injury to those individuals and employees or be required to pay fines or take other action with respect to judicial or regulatory actions arising out of such incidents. Data privacy or security breaches by employees and others with permitted access to our systems, including in some cases third-party service providers to which we may outsource certain business functions, may also pose a risk that sensitive data, including intellectual property or personal information, will be exposed to unauthorized persons or to the public.

We may not be able to attract and retain key management and other personnel.

In order to produce, develop, support and market our products, we depend on the expertise and leadership of our senior management team and other key members of our organization and need to attract and retain talent to support our operations in highly competitive markets or areas. The loss of key members of our organization, including senior members of our scientific and management teams, high-quality researchers and

development specialists, could delay or prevent the achievement of major business objectives. The market for such talent has become increasingly competitive, including in specific geographic regions and in specialized fields such as clinical development and biosciences, and we are required to invest heavily in the recruitment, training and retention of qualified individuals, including salary and other compensation to reward performance and incentivize employees. Despite our efforts to retain them, key employees could terminate their employment with us for any reason and there is no assurance that we will be able to attract or retain key employees and successfully manage them. Our inability to attract, integrate and retain highly skilled personnel, particularly those in leadership positions, may weaken our succession plans and may materially adversely affect our ability to implement our strategy and meet our strategic objectives, which could ultimately adversely affect our business and results of operations.

Legal and Regulatory Risks

We are involved in litigation relating to our operations on an ongoing basis, and such litigation could result in financial losses or harm our business.

We are involved in various litigation matters relating to our operations on an ongoing basis, including claims related to product liability, intellectual property and commercial disputes, as well as claims related to antitrust, sales and marketing and other regulatory regimes. Given the inherent unpredictability of litigation, it is possible that an adverse outcome in one or more pending or future litigation matters could have a material adverse effect on our operating results or cash flows. For a description of certain ongoing litigation, see Note 32 to our audited consolidated financial statements included in this annual report.

Our products may have unanticipated adverse effects or possible adverse effects, which may restrict use of the product or give rise to product liability claims.

As a pharmaceutical company, we are subject to significant risks related to product liability. Unanticipated adverse reactions or unfavorable publicity from complaints concerning any of our products, or those of our competitors, could have an adverse effect on our ability to obtain or maintain regulatory approvals or successfully market our products, and may even result in recalls, withdrawal of regulatory approval or adverse labeling of the product.

While our products are subject to comprehensive clinical trials and rigorous statistical analysis during the development process prior to approval, there are inherent limitations with regard to the design of such trials, including the limited number of patients enrolled in such trials, the limited time used to measure the efficacy of the product and the limited ability to perform long-term monitoring. In the event that such unanticipated adverse reactions are discovered, we may be required to add descriptions of the adverse reactions as precautions to the packaging of our products, recall and terminate sales of products or conduct costly post-launch clinical trials. Furthermore, concerns relating to potential adverse reactions could arise among consumers or medical professionals, and such concerns, whether justified or not, could have an adverse effect on sales of our products and our reputation. We could also be subject to product liability litigation by patients who have suffered, or claim to have suffered, such adverse reactions resulting in harm to their health.

Although we have from time to time maintained product liability insurance at coverage levels that we believe are appropriate, we could be subject to product liability that significantly exceeds our policy limits. Product liability coverage is also increasingly difficult and costly to obtain and may not be available in the future on acceptable terms. Therefore, it is possible that we may need to rely increasingly on self-insurance for the management of product liability risk. In cases where we self-insure, the legal costs that we would bear for handling such claims and potential indemnifications to be paid to claimants could materially and adversely affect our financial condition. In addition, the negative publicity from product liability claims, whether justified, may damage our reputation and may negatively impact the number of prescriptions of the product in question or our other products. As a result, our business, financial condition and results of operations could be materially and adversely affected.

We are subject to the risk of intellectual property infringement claims directed at us by third parties.

We are subject to the risk of infringement claims directed at us by third parties, even if we do not knowingly infringe on any valid third-party intellectual property rights. Although we monitor our operations to prevent infringement on the intellectual property rights of third parties, if we are found to have infringed the intellectual property rights of others or if we agree to settle infringement claims, we may be required to recall the relevant products, terminate manufacturing and sales of such products, pay significant damages or pay significant royalties.

We evaluate any such infringement claims to assess the likelihood of unfavorable outcomes and to estimate, if possible, the amount of potential losses. Based on these assessments and estimates, and in keeping with applicable accounting and disclosure standards, we establish reserves and/or disclose the relevant litigation claims or decide not to establish reserves or disclose litigation claims. These assessments and estimates are based on the information available to our management at such time and involve a significant amount of management judgment. Actual outcomes or losses may differ materially from those envisioned by our current assessments and estimates. Although the parties to such patent and intellectual property disputes in the pharmaceutical industry have often settled through licensing or similar arrangements, the costs associated with these arrangements may be substantial and could include the payment of ongoing royalties. Furthermore, the necessary licenses may not be available on acceptable terms or at all. Therefore, if we are unable to successfully defend against infringement claims by third parties, our financial results could be materially and adversely affected.

We are subject to evolving and complex tax and related risks, which may have a material adverse effect on our business, financial position and results of operations.

We are subject to evolving and complex tax laws in the jurisdictions in which we operate, and routinely obtain advice on tax-related matters, including in connection with the Shire Acquisition, where we assumed certain tax related risks related to the legacy Shire business, including the tax treatment of the break fee of 1.635 billion USD that Shire received in connection with the terminated offer to acquire Shire made by AbbVie, Inc. in 2014. The Irish Revenue Commissioners issued a tax assessment in November 2018 for 398 million EUR in respect of this fee. Takeda appealed the assessment to the Tax Appeals Commission ("TAC") and the appeal was heard by the TAC in late 2020. On July 30, 2021, Takeda received a ruling on the matter from the TAC, with the TAC ruling in favor of Irish Revenue Commissioners. Due to certain procedural matters which arose subsequently, the TAC is required to re-hear the matter. While Takeda continues to assert that the AbbVie break fee is not subject to Irish tax, Takeda has recorded a tax provision for 522 million EUR in current liabilities as income taxes payable, representing the 398 million EUR tax liability asserted by Irish Revenue Commissioners plus accrued interest for the fiscal year ended March 31, 2023.

Significant judgment is required in determining our tax liabilities, and our tax returns are periodically examined by various tax authorities. We regularly assess the likelihood of outcomes resulting from these examinations to determine the adequacy of its accrual for tax contingencies; however, due to the complexity of tax matters, the ultimate resolution of any tax matters may result in payments greater or less than the amounts accrued. In addition, we may be affected by changes in tax laws, including tax rate changes, new tax laws, and revised tax law interpretations in domestic and foreign jurisdictions and between jurisdictions, including by the EU, which could materially adversely affect our tax expense and/or tax balances, and changes in tax policies could materially adversely impact our business. The occurrence of any of these risks could have a material adverse effect on our business, financial position and results of operations.

The Organization for Economic Co-operation and Development (OECD) introduced a new inclusive framework on Base Erosion and Profit Shifting (BEPS 2.0) that contains a two pillar solution to address the tax challenges arising from the digitalization of the economy. These changes are now being progressively implemented by tax authorities around the world and represent a fundamental change to the international tax framework. Pillar One provides for a new nexus standard/taxing right that allocates a portion of intangible/residual profits directly to market jurisdictions but only for the largest and most profitable companies, including Takeda. Pillar Two provides for a global minimum level of taxation (15%) that establishes a floor for tax competition amongst jurisdictions. Since the introduction of the OECD Inclusive Framework, over 130 countries have endorsed the framework. On March 28, 2023 the Japanese Diet passed a tax reform bill containing laws to implement certain aspects of the OECD BEPS Pillar Two initiative. These provisions generally reflect the rules established by the OECD and will apply to fiscal years beginning on or after April 1, 2024. Takeda will review these newly enacted rules to determine the potential impact. It is possible that this may result in top-up taxes in some jurisdictions in which Takeda operates.

Changes in data privacy and protection laws and regulations or any failure to comply with such laws and regulations, could adversely affect our business and financial results.

We are subject to laws and regulations globally regarding privacy, data protection, and data security, including those related to the collection, storage, handling, use, disclosure, transfer, and security of personal data. Significant uncertainty exists as privacy and data protection laws may be interpreted and applied differently from country to country and may create inconsistent or conflicting requirements. For example, the EU's General Data Protection Regulation (the "GDPR") imposes significant data protection obligations on companies regarding the handling of personal data and provides individuals with heightened privacy rights. Since GDPR became effective in 2018, other countries have enacted or are in the process of drafting enhanced privacy laws, such as Brazil, California and other states in the U.S., Canada, China, India, Japan and Singapore. Of particular concern is China's Personal Information Protection Law, which became effective in November 2021, due to its stringent obligations, severe enforcement penalties and the unclarity of the law, where many of its obligations remain to be clarified or operationalized by the authorities. The EU has also imposed higher restrictions and obligations regarding the transfer of personal data outside the EU, which are attracting regulatory scrutiny and fines for companies operating in Europe Moreover, significant regulatory fines may be imposed on us for violation of these laws, particularly in the case of the GDPR, which are set at a maximum of the higher of 20 million EUR or 4% of annual global turnover for the most serious breaches.

The increased use of digital technologies involving personal data, such as mobile health apps, wearables, digitalization of clinical trials or artificial intelligence tools deployed on personal data pose additional risks for our company both in terms of the larger volume of personal data we handle but also in terms of potential security threats of such technology and our ability to assess the deployment of each technology because of the sheer volume and speed at which they are being developed. Compliance with existing, proposed and recently enacted laws and regulations can be costly; any failure to comply with these regulatory standards could also subject us to legal and reputational risks. Misuse of or failure to secure personal information could also result in violation of data privacy laws and regulations, legal proceedings against us by governmental entities or others or damage to our reputation and credibility and could also have a negative impact on our company results.

We may incur claims relating to our use, manufacture, handling, storage or disposal of hazardous materials.

Our research and development and manufacturing processes require the transportation, storage and use of hazardous materials, including chemicals and radioactive and biological materials, and may result in the generation of hazardous waste. National and local laws and regulations in many of the jurisdictions in which we operate impose substantial potential liability for the improper use, manufacture, handling, storage, transportation and disposal of hazardous materials as well as for land contamination, and, in some cases, this liability may continue over long periods of time. Despite our compliance efforts, we cannot eliminate the risk of industrial accidents that may lead to discharges or releases of hazardous materials and any resultant injury, property damage or environmental contamination from these materials. For example, real properties that we owned or used in the past or that we own or use now or in the future may contain detected or undetected contamination resulting from our operations at those sites or the activities of prior owners or occupants. We may suffer from expenses, claims or liability which may fall outside of or exceed our

insurance coverage.

Furthermore, changes to current environmental laws and regulations may impose further compliance requirements on us that may impair our research, development and production efforts as well as our other business activities. Examples of new or evolving regulatory requirements include REACH; Classification, Labelling, and Packaging of substances and mixtures ("CLP"); the Globally Harmonized System of Classification and Labelling of Chemicals ("GHS"); producer responsibility frameworks; and regulations related to addressing climate change or other emerging environmental areas. Increased environment, health and safety laws, regulations and enforcement could result in substantial costs and liabilities to us and could subject our use, manufacture, handling, storage, transportation, and disposal of hazardous materials to additional constraints. Consequently, compliance with these laws could result in capital expenditures as well as other costs and liabilities, thereby adversely affecting business, financial position and results of operations.

Risks Relating to the Operating Environment

Our results of operations and financial condition may be adversely affected by foreign currency exchange rate fluctuations.

We manufacture and sell products to customers in numerous countries, and we have entered and will enter into acquisition, licensing, borrowings or other financial transactions that give rise to translation and transaction risks related to foreign currency exposure. Fluctuations in currency exchange rates in the markets where we are active could negatively affect our results of operations, financial position and cash flows. For the fiscal year ended March 31, 2023, 87.3% of our sales were in markets outside Japan. Our consolidated financial statements are presented in Japanese yen, and by translating the foreign currency financial statements of our foreign subsidiaries into Japanese yen, the amounts of our revenue, operating profit, assets and equity, on a consolidated basis, are affected by prevailing rates of exchange.

We utilize certain hedging measures with respect to some of our foreign currency transactions. However, such hedging measures do not cover all of our exposures and, even to the extent they do, they may only delay, or may otherwise be unable to completely eliminate, the impact of fluctuations in foreign currency exchange rates.

Our business may be adversely affected by climate change, extreme weather events, earthquakes, civil or political unrest, terrorism or other catastrophic events.

We are exposed to both physical and transition risks (financial and regulatory driven risks) associated with climate change. To date, we have not experienced material impacts relating to climate change, including compliance or litigation-related impacts. However, in recent years, extreme weather events and changing weather patterns such as storms, flooding, droughts and temperature changes have become more common. As a result, we are potentially exposed to various natural disasters or extreme weather risks such as hurricanes, tornadoes, droughts or floods, typhoons, tidal waves, wildfires or other events that may result from the impact of climate change on the environment. Moreover, despite our internal evaluations regarding climate-related risks, there may be additional effects of climate change not currently contemplated by our internal models or by the market and society at large that may materialize in the future, leading to unexpected impacts on our business.

Climate change may also result in new or more stringent regulatory requirements globally. Climate-related regulations may require companies to accelerate and/or increase investment in technology to reduce energy consumption, water consumption and greenhouse gas emissions beyond current plans. Climate-related regulations could also lead to mandatory carbon pricing or climate risk disclosures. The net impact of these climate-related transition risks could increase our operational expenses or that of our suppliers. We have also established a number of initiatives relating to the environment voluntarily, including a commitment to achieve net-zero (as defined in the Science Based Targets initiative (SBTi) Corporate Net-Zero Standard) in greenhouse gas (GHG) emissions related to our operations (Scope 1 and Scope 2) before 2035 and for our entire value chain (including currently estimated Scope 3 GHG emissions) by 2040. See "*—Risks Relating to Our Business Strategies—We may experience difficulty implementing sustainability-related measures, particularly those relating to the environment, or in meeting the expectations of stakeholders.*"

In addition, Japan, the U.S. and other regions in the world where we operate are subject to the risk of natural disasters such as earthquakes, floods, tsunamis and/or volcanic eruptions. Other events outside our control, such as war, civil or political unrest, pandemics or the localized spread of new diseases, deliberate acts of sabotage, terrorism or industrial accidents such as fire and explosion, whether due to human or equipment error, could damage, cause operational interruptions, or otherwise adversely affect certain of our manufacturing or other facilities as well as potentially cause injury or death to our personnel. In the event of a major natural disaster or other uncontrollable event or accident, our facilities, particularly our production plants, may experience catastrophic loss, operations at such facilities may be halted, shipments of products may be suspended or delayed, trials or other research and development activities may be halted or otherwise affected and large losses and expenses to repair or replace facilities may be incurred. Such negative consequences could cause product shortages, significant losses of sales or require significant unexpected expenditures, and materially adversely affect our business, financial condition and results of operations. In addition, our business may also be adversely affected if our suppliers or business partners were to experience a catastrophic loss due to natural disasters, terrorism, accidents or other uncontrollable events.

Although we purchase comprehensive global insurance to cover property damage and consequent business interruption for certain potential losses at sites owned by us and at certain critical supplier sites, we do not maintain insurance policies to cover all potential losses and therefore our insurance policies may not be adequate to cover all possible losses and expenses. For instance, we do not maintain earthquake insurance in Japan.

Social media platforms and new technologies present risks and challenges for our reputation and business.

Consumers, the media, pharmaceutical companies and other parties increasingly use social media to communicate about pharmaceutical products and the diseases they are intended to treat, and may use other, newer technologies in a similar way in the future. For pharmaceutical companies, the use of these technologies requires specific attention, monitoring programs and moderation of comments. For example, negative or inaccurate posts or comments about us or our products on any social media networking platforms could damage our reputation and business. Social media could also be used to bring negative attention to us or to the pharmaceutical industry as a whole, which could in turn cause reputational harm to us and negatively impact our business. The nature of evidence-based health care, however, may prevent us from rapidly and adequately defending our interests against such comments. In addition, our employees and partners may use social media and other digital platforms and mobile technologies inappropriately or in ways that violate applicable laws or our internal policies, which may expose us to liability, or which could lead to breaches of data security, loss of trade secrets or other intellectual property or public disclosure of sensitive information, including information about our employees, clinical trial subjects or customers.

Other Risks Affecting Our Business

Sales to wholesalers are concentrated, which exposes us to credit risks and pricing pressures.

A significant portion of our global sales are made to a relatively small number of wholesale distributors, retail chains and other purchasing groups. In the fiscal year ended March 31, 2023, there were three wholesale distributors, AmerisourceBergen Corporation, McKesson Corporation and Cardinal Health, Inc., that each individually accounted for over ten percent of Takeda's total revenue. If one of our significant wholesale distributors encounters financial or other difficulties, such a distributor may decrease the amount of business that it does with us, and we may be unable to collect the amounts that the distributor owes us on a timely basis or at all. Furthermore, the concentration of wholesale distributors has been increasing through mergers and acquisitions. In addition to increased credit risks, this has resulted in such distributors gaining additional purchasing leverage, which may increase pricing pressure on our products. Such credit concentration risks and pricing pressure could adversely affect our business, financial condition and results of operations.

We may have to recognize additional charges on our statements of profit or loss due to impairment of goodwill, other intangible assets and equity method investments.

We carry significant amounts of goodwill and intangible assets on our consolidated statements of financial position as a result of past acquisitions, including the Shire Acquisition. As of March 31, 2023, we had goodwill of 4,790.7 billion JPY and intangible assets of 4,269.7 billion JPY. Goodwill and intangible assets recorded in relation to acquisitions are recognized on our consolidated statements of financial position on the acquisition date. Under IFRS, we are required to examine such assets for impairment annually or whenever events or changes in circumstances indicate that the carrying amount of an asset may not be recoverable. See Item 5. Operating and Financial Review and Prospects—A. Operating Results-Critical Accounting Policies-Impairment of Goodwill and Intangible Assets.

We occasionally enter into business ventures with third-party entities where we have significant influence over the decisions on financial and operating policies, but do not have control or joint control (referred to as investments in associates). We also enter into joint arrangements whereby we and the other parties that have joint control of the arrangement have rights to the net assets of the arrangement (referred to as joint venture). We account for these investments using the equity method of accounting. As of March 31, 2023, the carrying amount of investments accounted for using the equity method was 99.2 billion JPY. Under IFRS, at each reporting period, we are required to determine whether there is objective evidence that the investment in each associate or joint venture is impaired.

The recognition of such impairment charges may adversely affect our business, financial condition and results of operations.

Risks Relating to the ADSs

A holder of ADSs has fewer rights than a holder of our common stock has, and a holder of ADSs has to act through the depositary to exercise those rights.

The rights of shareholders under Japanese law to take various actions, including voting their shares, receiving dividends and distributions, bringing derivative actions, examining a company's accounting books and records and exercising appraisal rights, are available only to holders of record. Because the depositary, through its custodian agents, is the record holder of the shares underlying the ADSs, only the depositary can exercise those rights in connection with the deposited shares. Pursuant to the deposit agreement, the depositary will endeavor, to the extent practicable, to make efforts to vote or cause to be voted the shares underlying the ADSs as instructed by the holders and will pay to the holders the dividends and distributions collected from the Company. The depositary and its agents may not be able to send voting instructions to holders of ADSs or carry out their voting instructions in a timely manner. Furthermore, the depositary and its agents will not be responsible for any failure to carry out any instructions to vote, for the manner in which any vote is cast or for the effect of any such vote. As a result, holders of ADSs may not be able to exercise their right to vote. Moreover, in the capacity as an ADS holder, such a holder will not be able to bring a derivative action, examine the Company's accounting books or records or exercise appraisal rights except through the depositary.

Rights of shareholders under Japanese law may be more limited than under the laws of other jurisdictions.

Our Articles of Incorporation, Board of Directors Charter, Audit and Supervisory Committee Charter and the Companies Act govern our corporate affairs. Legal principles relating to such matters as the validity of corporate procedures, directors' and officers' fiduciary duties, and shareholders' rights may be different from those that would apply to a non-Japanese company. Shareholders' rights under Japanese law may not be as extensive as shareholders' rights under the laws of other jurisdictions. ADS holders may have more difficulty in asserting their rights as a shareholder than such holders would as shareholders of a corporation organized in another jurisdiction. In addition, Japanese courts may not be willing to enforce liabilities against the Company in actions brought in Japan that are based upon the securities laws of other jurisdictions.

Because of daily price range limitations under Japanese stock exchange rules, a holder of ADSs who has surrendered his or her ADSs in favor of shares of our common stock may not be able to sell his/her shares of our common stock at a particular price on any particular trading day, or at all.

Stock prices on Japanese stock exchanges are determined on a real-time basis by the equilibrium between bids and offers. These exchanges are order-driven markets without specialists or market makers to guide price formation. To prevent excessive volatility, these exchanges set daily upward and downward price fluctuation limits for each stock, based on the previous day's closing price. Although transactions may continue at the upward or downward limit price if the limit price is reached on a particular trading day, no transactions may take place outside these limits. Consequently, a holder of ADSs who has surrendered his or her ADSs in favor of shares of our common stock wishing to sell on a Japanese stock exchange at a price above or below the relevant daily limit may not be able to sell his or her shares at such price on a particular trading day, or at all.

U.S. investors may have difficulty in serving process or enforcing a judgment against us or our directors or executive officers.

We are a limited liability, joint stock corporation incorporated under the laws of Japan. Many of our directors and executive officers reside in Japan, Europe or elsewhere outside of the U.S., and a large portion of our assets and the assets of these persons are located in Japan and elsewhere outside the U.S. It may not be possible, therefore, for U.S. investors to effect service of process within the U.S. upon us or these persons or to enforce against us or these persons judgments obtained in U.S. courts predicated upon the civil liability provisions of the federal securities laws of the U.S. There is doubt as to the enforceability in Japan, in original actions or in actions for enforcement of judgment of U.S. courts, of liabilities predicated solely upon the federal securities laws of the U.S.

Investors holding less than a full unit of shares will have limited rights as shareholders.

Our Articles of Incorporation provide that 100 shares of our common stock constitute one unit. Although holders of ADSs may withdraw shares of our common stock constituting less than one unit, in connection with the direct holding of the shares of our common stock, the Companies Act imposes significant restrictions and limitations on holders of shares of our common stock that do not constitute a full unit. In general, holders of shares of our common stock constituting less than one unit do not have the right to vote with respect to those shares.

Dividend payments and the amount you may realize upon a sale of our ADSs will be affected by fluctuations in the exchange rate between the U.S. dollar and the Japanese yen.

Cash dividends, if any, in respect of the shares of our common stock represented by our ADSs will be paid to the depositary in Japanese yen and then converted by the depositary into U.S. dollars, subject to certain conditions. Accordingly, fluctuations in the exchange rate between the Japanese yen and the U.S. dollar will affect, among other things, the U.S. dollar amounts a holder of ADSs will receive from the depositary in respect of dividends, the U.S. dollar value of the proceeds that a holder of ADSs would receive upon sale in Japan of the shares of our common stock obtained upon surrender of ADSs and the secondary market price of ADSs.

Our shareholders of record on a given record date may not receive the dividend they anticipate.

The customary dividend payout practice of publicly listed companies in Japan may significantly differ from the practices widely followed or otherwise deemed necessary or fair in foreign markets. We ultimately have a discretion to determine any dividend payment amount to our shareholders of record as of a record date, including whether we will make any dividend payment to such shareholders at all, only after such record date. For that reason, our shareholders of record on a given record date may not receive the dividends they anticipate.

ADS holders may not be entitled to a jury trial with respect to claims arising under the deposit agreement, which could result in less favorable outcomes to the plaintiff(s) in any such action.

The deposit agreement governing the ADSs provides that, to the fullest extent permitted by law, ADS holders waive the right to a jury trial for any claim they may have against us or the depositary arising out of or relating to our shares, the ADSs or the deposit agreement, which may include any claim under the U.S. federal securities laws.

If we or the depositary were to oppose a jury trial based on this waiver, the court would have to determine whether the waiver was enforceable based on the facts and circumstances of the case in accordance with applicable state and federal law. To our knowledge, the enforceability of a contractual pre-dispute jury trial waiver in connection with claims arising under the federal securities laws has not been finally adjudicated by the U.S. Supreme Court. However, we believe that a contractual pre-dispute jury trial waiver provision is generally enforceable, including under the laws of the State of New York, which govern the deposit agreement, or by a federal or state court in the City of New York, which has jurisdiction over matters arising under the deposit agreement. In determining whether to enforce a contractual pre-dispute jury trial waiver, courts will generally consider whether a party knowingly, intelligently and voluntarily waived the right to a jury trial. We believe that this would be the case with respect to the deposit agreement and the ADSs. It is advisable that prospective investors consult legal counsel regarding the jury waiver provision before investing in the ADSs.

As a result, if a holder or beneficial owner of ADSs brings a claim against us or the depositary in connection with matters arising under the deposit agreement or the ADSs, including claims under federal securities laws, such a holder or beneficial owner may not be entitled to a jury trial with respect to such claims, which may have the effect of limiting and discouraging lawsuits against us or the depositary. If a lawsuit is brought against us or the depositary under the deposit agreement, it may be heard only by a judge or justice of the applicable trial court, which would be conducted according to different civil procedures and may result in different outcomes than a trial by jury would have, including outcomes that could be less favorable to the plaintiff(s) in any such action.

Nevertheless, if this jury trial waiver is not enforced under applicable law, an action could proceed under the terms of the deposit agreement with a jury trial. No condition, stipulation or provision of the deposit agreement or the ADSs serves as a waiver by any holder or beneficial owner of ADSs or by us or the depositary of compliance with any substantive provision of the U.S. federal securities laws and the rules and regulations promulgated thereunder.

Item 4. Information on the Company

A. History and Development of the Company

Takeda is a global, values-based, R&D-driven biopharmaceutical company with a diverse portfolio, engaged primarily in the research, development, production and global commercialization of pharmaceutical products. Takeda focuses on five key business areas: Gastroenterology ("GI"), Rare Diseases, Plasma-Derived Therapies ("PDT") Immunology, Oncology and Neuroscience. Our R&D efforts are focused on four therapeutic areas: Gastrointestinal and Inflammation, Neuroscience, Oncology, and Rare Genetics and Hematology. We also make targeted R&D investments in PDT and Vaccines. We focus on developing innovative medicines that make a difference in people's lives by advancing the frontier of new treatment options and leveraging our collaborative R&D engine and capabilities to create a robust, modality-diverse pipeline. We focus on the highest unmet need, both in rare and more prevalent conditions, to deliver high-quality medicines and vaccines to patients and communities as quickly as possible. We have a presence in approximately 80 countries and regions, a network of manufacturing sites around the world, and major research centers in Japan and the United States.

We are also committed to our three imperatives powered by data, digital and technology. Patient - We responsibly translate science into highly innovative, life-transforming medicines and vaccines, and accelerate access to improve lives worldwide. People - We create an exceptional people experience. Planet - We protect our planet.

Our 242-year history started in 1781, when Chobei Takeda began selling traditional Japanese and Chinese herbal medicines in Doshomachi, Osaka. After Japan's Meiji Restoration opened the country to increase overseas trade in the late 1860s, we were one of the first companies to begin importing western medicines into Japan. In 1895, we began our pharmaceutical manufacturing business, and our research division was formed in 1914, allowing us to begin to discover our own pharmaceutical products. In 1925, we were incorporated as Chobei Takeda & Co., Ltd. and our name was later changed to Takeda Pharmaceutical Company Limited. In 1949, our shares were listed on the Tokyo and Osaka stock exchanges. We began expanding into overseas markets in the 1960s, first in Asia and, subsequently, other markets around the world. We began enhancing our overseas business infrastructure in the late 1990s, with the formation of new subsidiaries in the U.S. and Europe.

In 2008, we acquired a leading U.S. biopharmaceutical company in Millennium Pharmaceuticals, Inc. We leveraged the complementary strengths of Millennium and Takeda, with Millennium's innovative products, pipeline and expertise in oncology. Takeda also acquired Nycomed in 2011, with a strong presence in Europe and emerging markets. This allowed Takeda to expand to over 70 markets and enhance its global sales structure in order to deliver pharmaceutical products to more patients around the world. These two large acquisitions within a short time span allowed Takeda to accelerate its globalization.

Since 2014, our efforts have been focused on enhancements to our R&D capabilities, prudent value enhancing acquisition activities and post-acquisition integration. Specifically, Takeda implemented an R&D transformation process to diversify modalities in our research, actively engage with innovative ecosystems around the world in the form of partnerships, and focus on our core therapeutic areas of Gastrointestinal and Inflammation, Neuroscience, Oncology, and Rare Genetics and Hematology. As examples of acquisition activities, in January 2019, we acquired Shire Plc., bringing together Takeda and Shire's complementary positions in gastroenterology and neuroscience, and establishing leading positions in rare diseases and PDT. In February 2023, we acquired all shares of Nimbus Lakshmi, Inc., a subsidiary of Nimbus Therapeutics, LLC, which brought into our pipeline TAK-279, a highly selective oral TYK2 inhibitor with potential to demonstrate best-in-class efficacy, safety and convenience in the treatment of psoriasis as well as multiple other immune-mediated diseases, including inflammatory bowel disease, psoriatic arthritis and systemic lupus erythematosus.

During the three fiscal years ended March 31, 2023, we also divested several businesses and assets in non-core areas. See Item 5. Operating and Financial Review and Prospects—A. Operating Results for further details on major businesses and assets acquired and divested.

Our principal capital expenditures during the three fiscal years ended March 31, 2023 consisted of additions to property, plant and equipment and intangible assets. In the fiscal years ended March 31, 2021, 2022 and 2023, we made capital expenditures (consisting of the additions to property, plant and equipment and intangible assets recorded on our consolidated statements of financial position) of 330.7 billion JPY, 239.9 billion JPY and 898.7 billion JPY, respectively, including the following highlights:

- In the fiscal year ended March 31, 2021, we invested in a 24,000 square-foot cell therapy manufacturing facility in Cambridge, Massachusetts allowing for the production of clinical-grade material to enable clinical development through pivotal phase 2b trials. We continued to invest in our dengue vaccine candidate manufacturing plant in Singen, Germany, and our oncology and gastroenterology manufacturing site in Tianjin, China, as well as expanding our plasma collection center network, with the addition of 26 new centers in the U.S. and Europe to bring Takeda's total footprint to 181 centers. We also executed several in-licensing deals to strengthen the pipeline, including TAK-999 from Arrowhead Pharmaceuticals Inc., and soticlestat from Ovid Therapeutics Inc.

- In the fiscal year ended March 31, 2022, we broke ground on the first 'net zero carbon emissions' building in our global network marking a first-of-its-kind investment within the biotechnology industry in Singapore. The building, a 14 million USD expansion of Takeda's manufacturing operations in Singapore has been in operation since the end of 2022. We also continued investing in our plasma collection center network, with the addition of 23 new centers in the U.S. and Europe to bring Takeda's total footprint to 204 centers.
- In the fiscal year ended March 31, 2023, we continued investing in our plasma collection center network, with the addition of 29 new centers in the U.S. and Europe to bring Takeda's total footprint to 233 centers. We also executed several in-licensing deals and an acquisition to strengthen the pipeline, including TAK-279 from Nimbus Therapeutics, LLC, fruquintinib from HUTCHMED Limited, and TAK-227 from Zedira GmbH and Dr. Falk Pharma GmbH.

We currently have various capital expenditure projects in process, including the continued expansion of production capacity in our plasma manufacturing network and the projects described in Item 4.D. (Property, Plant and Equipment). We are primarily financing these projects with funds on hand. For additional information on our ongoing capital expenditure projects, see Note 10 and Note 12 to our audited consolidated financial statements.

The address of our global head office is 1-1, Nihonbashi-Honcho 2-Chome, Chuo-ku, Tokyo, 103-8668, Japan; telephone number: 81-3-3278-2111. Takeda's agent in the U.S. in connection with this annual report is Takeda Pharmaceuticals U.S.A., Inc., 99 Hayden Avenue, Lexington, MA 02421 U.S.A., telephone number: 1-617-349-0200.

The SEC maintains an internet site that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC at www.sec.gov. As a foreign private issuer, we are exempt from the rules under the Exchange Act prescribing the furnishing and content of proxy statements to shareholders. Our corporate website is www.takeda.com.

B. Business Overview

We are a patient-focused, values-based, R&D-driven global biopharmaceutical company with a diverse portfolio, engaged primarily in the research, development, production and global commercialization of pharmaceutical products. Our intent is to translate science into highly innovative life transforming medicines. We have built an R&D engine focused on four therapeutic areas, leveraging internal research and external partners in order to have access to different modalities like biologics or cell therapy. We have a geographically diversified global business base and our prescription drugs are marketed worldwide.

We have approximately 49,000 employees worldwide dedicated to our purpose of better health for people and a brighter future for the world through leading innovation in medicine. Our culture is based on our values of Takeda-ism which incorporates Integrity, Fairness, Honesty, and Perseverance, with Integrity at the core. They are brought to life through actions based on Patient-Trust-Reputation-Business, in that order.

Our commercial efforts are focused on five key business areas of GI, Rare Diseases, PDT, Oncology, and Neuroscience, which in the fiscal year ended March 31, 2023 accounted for 88.7% of our total revenue. We believe these five business areas will drive our future revenue growth, and we will continue to make the necessary investments to maximize our portfolios in these areas. Our growth driver products in our key business areas include the following Growth & Launch Products: *ENTYVIO*, *ALOFISEL, TAKHZYRO, LIVTENCITY, GAMMAGARD LIQUID/KIOVIG, HYQVIA, CUVITRU, ALBUMIN/FLEXBUMIN, ALUNBRIG* and *EXKIVITY*. We have also been making targeted acquisitions and divestitures to further sharpen our focus on these key business areas, and plan to continue to refine our portfolio going forward.

Our R&D engine is focused on translating science into highly innovative, life-changing medicines that make a critical difference to patients. Takeda supports dedicated R&D efforts across three areas: Innovative Biopharma, Plasma-Derived Therapies ("PDT") and Vaccines. The R&D engine for Innovative Biopharma is the largest component of our R&D investment and has produced exciting new molecular entities ("NMEs") that represent potential best-in-class and/or first-in-class medicines in areas of high unmet medical need across our core therapeutic areas (Gastrointestinal and inflammation, neuroscience, oncology, and rare genetics and hematology). We are working to harness the potential of cell and gene therapies by investing in new capabilities and next-generation platforms internally and through a network of partnerships. We are embracing data and digital technologies to improve the quality of innovation and accelerate execution.

We are also focused on optimizing our financial strength, delivering competitive margins and generating cash flows to invest in the business, to maintain a solid investment grade credit rating and to return cash to shareholders.

The following is a summary of our principal products by key business area.

In GI, our principal products include:

- *ENTYVIO* (vedolizumab), a treatment for moderate to severe ulcerative colitis and Crohn's disease. Sales of *ENTYVIO* have grown strongly since its launch in the U.S. and Europe in 2014 and was our top selling product in the fiscal year ended March 31, 2023. *ENTYVIO* is now approved in more than 70 countries worldwide. We strive to maximize its potential by seeking approval in additional countries, examining use in further indications, while also pursuing a subcutaneously administered formulation. In the fiscal year ended March 31, 2023, our revenue from *ENTYVIO* was 702.7 billion JPY.
- *ALOFISEL* (darvadstrocel), a treatment for complex perianal fistulas in adult patients with nonactive/mildly active luminal Crohn's disease, when fistulas have shown an inadequate response to at least one conventional or biologic therapy. *ALOFISEL* was approved in Europe in 2018, becoming the first allogeneic stem cell therapy to receive central marketing authorization approval in Europe. *ALOFISEL* was also approved in Japan in 2021. In the fiscal year ended March 31, 2023, our revenue from *ALOFISEL* was 2.7 billion JPY.
- *TAKECAB/VOCINTI* (vonoprazan fumarate), a treatment for acid-related diseases. *TAKECAB* was launched in Japan in 2015 and has achieved significant growth driven by its efficacy in reflux esophagitis and the prevention of recurrence of gastric and duodenal ulcers during low-dose aspirin administration. *TAKECAB* (Chinese brand name: *VOCINTI*) was approved for reflux esophagitis in 2019 in China. In the fiscal year ended March 31, 2023, our revenue from *TAKECAB/VOCINTI* was 108.7 billion JPY.
- *GATTEX/REVESTIVE* (teduglutide[rDNA origin]), a treatment for patients with short bowel syndrome (SBS) who are dependent on parenteral support. *GATTEX/REVESTIVE* has been launched in the U.S., Europe, and Japan with adult and pediatric indications. In the fiscal year ended March 31, 2023, our revenue from *GATTEX/REVESTIVE* was 93.1 billion JPY.
- *DEXILANT* (dexlansoprazole), a treatment for gastric acid-related disorders such as healing of all grades of erosive esophagitis (EE), maintaining healing of EE and relief of heartburn and treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD), while having grown temporarily this fiscal year, is expected to continue its overall downtrend in revenue due to generic competition. In the fiscal year ended March 31, 2023, our revenue from *DEXILANT* was 69.4 billion JPY.

In Rare Diseases, our principal products are:

- *TAKHZYRO* (lanadelumab-flyo), for the prevention of hereditary angioedema (HAE) attacks. *TAKHZYRO* is a fully human monoclonal antibody that specifically binds and decreases plasma kallikrein, an enzyme which is chronically uncontrolled in people with HAE. *TAKHZYRO* was approved in both the U.S. and Europe in 2018, in China in 2020, and in Japan in 2022 and we are working to expand into further geographic areas. In the fiscal year ended March 31, 2023, our revenue from *TAKHZYRO* was 151.8 billion JPY.
- *LIVTENCITY* (maribavir), a treatment for adults and pediatric patients (12 years of age and older and weighing at least 35 kg) for post-transplant cytomegalovirus (CMV) infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, foscarnet or cidofovir. *LIVTENCITY* launched in the U.S. in December 2021, and was approved in Europe in November 2022. Early uptake has been strong as the first and only antiviral agent that targets and inhibits the pUL97 protein kinase and its natural substrates. In the fiscal year ended March 31, 2023, our revenue from *LIVTENCITY* was 10.5 billion JPY.
- *ELAPRASE* (idursulfase), an enzyme replacement therapy for the treatment of Hunter syndrome (also known as Mucopolysaccharidosis Type II or MPS II). In the fiscal year ended March 31, 2023, our revenue from *ELAPRASE* was 85.3 billion JPY.
- *REPLAGAL* (agalsidase alfa), an enzyme replacement therapy for the treatment of Fabry disease, marketed outside of the U.S., and also approved in China in 2020. Additionally, Takeda has acquired the manufacturing and marketing approval and the marketing rights of *REPLAGAL* in Japan from Sumitomo Dainippon Pharma as of February, 2022. Fabry disease is a rare, inherited genetic disorder resulting from a deficiency in the activity of the lysosomal enzyme alpha-galactosidase A, which is involved in the breakdown of fats. In the fiscal year ended March 31, 2023, our revenue from *REPLAGAL* was 66.7 billion JPY.
- *ADVATE* (antihemophilic factor (recombinant)), a treatment for hemophilia A (congenital factor VIII deficiency) for control and prevention of bleeding episodes, for perioperative management, and routine prophylaxis to prevent or reduce the frequency of bleeding episodes. In the fiscal year ended March 31, 2023, our revenue from *ADVATE* was 118.2 billion JPY.
- *ADYNOVATE/ADYNOVI* (antihemophilic factor (recombinant) [PEGylated]), an extended half-life recombinant factor VIII treatment for hemophilia A. *ADYNOVATE/ADYNOVI* uses the same manufacturing process as the standard half-life recombinant factor VIII therapy *ADVATE,* and adds a proven technology, PEGylation (a chemical process that prolongs the amount of time a compound remains in circulation, potentially allowing for fewer injections), which we exclusively licensed from Nektar Therapeutics. In the fiscal year ended March 31, 2023, our revenue from *ADYNOVATE/ADYNOVI* was 66.6 billion JPY.

In Plasma-Derived Therapies (PDT) Immunology, our principal products are:

- *GAMMAGARD LIQUID/KIOVIG* (Immune Globulin Intravenous (Human) 10%), a liquid formulation of the antibody replacement therapy immunoglobulin (IG), for the treatment of adult and pediatric patients two years of age or older with primary immunodeficiencies (PID) (administered either intravenously or subcutaneously), and adult patients with multifocal motor

neuropathy (MMN) (administered intravenously). *KIOVIG* is the brand name used for *GAMMAGARD LIQUID* in many countries outside of the U.S. *KIOVIG* is approved in Europe for patients with PID and certain secondary immunodeficiencies, and for adults with MMN.

- *HYQVIA* (Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase), a product consisting of human normal IG and recombinant human hyaluronidase (licensed from Halozyme). *HYQVIA* is the only subcutaneous IG treatment for PID patients with a dosing regimen that requires only one infusion up to once per month and one injection site per infusion to deliver a full therapeutic dose of IG. *HYQVIA* is approved in the U.S. for adults with PID, and in Europe for patients with PID syndromes and myeloma or CLL with severe secondary hypogammaglobulinemia and recurrent infections.
- *CUVITRU* (Immune Globulin Subcutaneous (Human), 20% Solution), indicated as replacement therapy for primary humoral immunodeficiency in adult and pediatric patients two years of age and older. *CUVITRU* is also indicated in Europe for the treatment of certain secondary immunodeficiencies. *CUVITRU* is the only 20% subcutaneous IG treatment option without proline and with the ability to infuse up to 60 mL (12 grams) per site and 60 mL per hour, per site as tolerated, resulting in fewer infusion sites and shorter infusion durations compared to other conventional subcutaneous IG treatments.

  In the fiscal year ended March 31, 2023, the total revenue from our PDT immunology portfolio, including *GAMMAGARD LIQUID/ KIOVIG, HYQVIA,* and *CUVITRU*, was 522.2 billion JPY.
- *FLEXBUMIN* (Human Albumin in a bag) and Human Albumin (glass), available as 5% and 25% solutions, indicated for hypovolemia, hypoalbuminemia due to general causes and burns, and for use during cardiopulmonary bypass surgery as a component of the pump prime. *FLEXBUMIN* 25% is also indicated for hypoalbuminemia associated with adult respiratory distress syndrome (ARDS) and nephrosis, and hemolytic disease of the newborn (HDN). In the fiscal year ended March 31, 2023, the total revenue from our albumin portfolio, including *FLEXBUMIN* and Human Albumin (glass) was 121.4 billion JPY.

In Oncology, our principal products include:

- *ALUNBRIG* (brigatinib), an orally administered small molecule anaplastic lymphoma kinase (“ALK”) inhibitor used to treat ALK-positive non-small cell lung cancer (NSCLC), was granted accelerated approval in the U.S. in 2017, marketing authorization in Europe in 2018 and in Japan in 2021. The indication of *ALUNBRIG* was expanded to include newly diagnosed ALK-positive NSCLC patients, first in the U.S. in May 2020. *ALUNBRIG* was also approved in China in March 2022. In the fiscal year ended March 31, 2023, our revenue from *ALUNBRIG* was 20.6 billion JPY.
- *EXKIVITY* (mobocertinib), a treatment for locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum based chemotherapy, was granted accelerated approval in the U.S. in September 2021, and China National Medical Products Administration (NMPA) approval in January 2023. Since its launch we are seeing rapid uptake in both the academic and community settings. In the fiscal year ended March 31, 2023, our revenue from E*XKIVITY* was 3.7 billion JPY.
- *LEUPLIN/ENANTONE* (leuprorelin), a treatment for hormone-responsive cancers such as prostate cancer or breast cancer in women, as well as children with central precocious puberty, women with endometriosis, infertility, and to improve anemia in women with uterine leiomyomata (fibroids). While leuprorelin is no longer protected by patent, there is limited generic competition due to manufacturing considerations. In the fiscal year ended March 31, 2023, our revenue from *LEUPLIN/ENANTONE* was 111.3 billion JPY.
- *NINLARO* (ixazomib), the first oral proteasome inhibitor for the treatment of multiple myeloma (MM), was approved in the U.S. in 2015 for relapsed/refractory MM and was approved in Europe in 2016, in Japan in 2017, and in China in 2018. In Japan, *NINLARO* is also approved as a maintenance treatment for MM. In the fiscal year ended March 31, 2023, revenue from *NINLARO* was 92.7 billion JPY.
- *ADCETRIS* (brentuximab vedotin), an anti-cancer agent used to treat Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL), has received marketing authorization in more than 70 countries worldwide and was approved in China in May 2020. We jointly developed *ADCETRIS* with Seagen Inc. and have commercialization rights in countries outside the U.S. and Canada. In the fiscal year ended March 31, 2023, our revenue from *ADCETRIS* was 83.9 billion JPY.

In Neuroscience, our principal products are:

- *VYVANSE/ELVANSE* (lisdexamfetamine dimesylate), a stimulant medication indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in patients aged six and above, and for the treatment of moderate to severe binge eating disorder in adults. However, sales are expected to decline due to generic competition in the U.S. in 2023. In the fiscal year ended March 31, 2023, our revenue from *VYVANSE/ELVANSE* was 459.3 billion JPY.
- *TRINTELLIX* (vortioxetine), an antidepressant indicated for the treatment of major depressive disorder (MDD) in adults. *TRINTELLIX* was co-developed with H. Lundbeck A/S, and Takeda has commercialization rights in the U.S., where it was launched in 2014 and in Japan, where it was launched in 2019. In the fiscal year ended March 31, 2023, our revenue from *TRINTELLIX* was 100.1 billion JPY.

For a breakdown of revenues by geographic region, see Note 4 to our audited consolidated financial statements.

Takeda's Initiatives to Mitigate the Impact of COVID-19

Three years have passed since the outbreak of COVID-19. As vaccines and therapies have become broadly available in many countries, governments are relaxing strict measures to prevent the spread of infection, such as travel restrictions. We will continue to adhere to local public health guidance in addition to the internal protocols and monitor any potential impacts of the effects of COVID-19, including new variants, on our business activities, with the intent to protect employees' health and safety, and to ensure our medicines are available to patients who rely on them.

In the fiscal year ended March 31, 2023, Takeda manufactured NUVAXOVID Intramuscular Injection, a novel recombinant protein-based COVID-19 vaccine which was licensed, with manufacturing technologies transferred, from Novavax, at its Hikari facility and distributed it in Japan. Takeda is working with Novavax to develop vaccines against the future variants including the Omicron variant. Takeda will also continue to provide distribution support in bringing an mRNA COVID-19 bivalent vaccine, SPIKEVAX Intramuscular Injection (Omicron targeting bivalent vaccine), to Japan through its partnership with Moderna.

Research and Development

Research and development expenses for the fiscal year ended March 31, 2023 were 633.3 billion JPY.

The research and development (R&D) of biopharmaceutical products is a lengthy and expensive process that can span more than 10 years. The process includes multiple studies to evaluate a product’s efficacy and safety, followed by submission to regulatory authorities who review the data and decide whether to grant marketing approval. Only a small number of therapeutic candidates pass such rigorous investigation and become available for use in clinical treatment. Once approved, there is ongoing R&D support for marketed products, including life-cycle management, medical affairs, and other investments.

Clinical trials, which must comply with regional and international regulatory guidelines, generally take five to seven years or longer, and require substantial expenditures. In general, clinical trials are performed in accordance with the guidelines set by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. The relevant regional regulatory authorities are the Food and Drug Administration (FDA) for the United States, the European Medicines Agency (EMA) for the EU, the Ministry of Health, Labour and Welfare (MHLW) for Japan and National Medical Products Administration (NMPA) for China.

The three phases of human clinical trials, which may overlap with each other, are as follows:

Phase 1 (“P-1”) clinical trials
Conducted using a small group of healthy adult volunteers in order to evaluate safety and absorption, distribution, metabolism and excretion of the drug.

Phase 2 (“P-2”) clinical trials
Conducted using a small group of patient volunteers in order to evaluate safety, efficacy, dosage and administration methods. P-2 clinical trials may be divided into two sub-categories, P-2a and P-2b. P-2a are usually pilot studies designed to demonstrate clinical efficacy or biological activity. P-2b studies look to find the optimum dose at which the drug shows biological activity with minimal side-effects.

Phase 3 (“P-3”) clinical trials
Conducted using a large number of patient volunteers in order to evaluate safety and efficacy in comparison to other medications already available or placebo.

Of these three phases, Phase 3 requires the largest expenditures and thus the decision to proceed with Phase 3 testing is a critical business decision in the drug development process. For those drug candidates that pass Phase 3 clinical trials, a New Drug Application ("NDA"), Biologics License Application (“BLA”) or a Marketing Authorization Application (“MAA”) is submitted to the relevant governmental authorities for approval, which if granted permits the subsequent launch of the drug. The preparation of an NDA, BLA or MAA submission involves considerable data collection, verification, analysis and expense. Even after the launch of the product, health authorities require post-marketing surveillance of adverse events, and they may request a post-marketing study to provide additional information regarding the risks and benefits of the product.

Takeda’s R&D engine is focused on translating science into highly innovative, life-changing medicines that make a critical difference to patients. Takeda supports dedicated R&D efforts across three areas: Innovative Biopharma, Plasma-Derived Therapies (“PDT”) and Vaccines. The R&D engine for Innovative Biopharma is the largest component of our R&D investment and has produced exciting new molecular entities (“NMEs”) that represent potential best-in-class and/or first-in-class medicines in areas of high unmet medical need across our core therapeutic areas (Gastrointestinal and inflammation, neuroscience, oncology, and rare genetics and hematology). We are working to harness the potential of cell and gene therapies by investing in new capabilities and next-generation platforms internally and through a network of partnerships. We are embracing data and digital technologies to improve the quality of innovation and accelerate execution.

Takeda’s pipeline is positioned to support both the near-term and long-term sustained growth of the company. Once first approval of a product is achieved, Takeda R&D is equipped to support geographic expansions of such approval and approvals in additional indications, as well as post-marketing commitment and potential additional formulation work. Takeda’s R&D team works closely with the commercial functions to maximize the value of marketed products and reflect commercial insights in its R&D strategies and portfolio.

In addition to our concentrated efforts to increase our in-house R&D capabilities, external partnerships with third-party partners are a key component of our strategy for enhancing our R&D pipeline. Our strategy to expand and diversify our external partnerships allows us to take part in research of a wide variety of new products and increases the chances that we will be able to take part in a major research-related breakthrough.

Our key in-house R&D facilities include:

- *Greater Boston Area Research and Development Site*: Our Boston R&D site is located in Cambridge, Massachusetts in the United States. It is the center of our global gastrointestinal and inflammation, oncology, and rare genetics and hematology R&D, and also supports R&D in other areas including plasma-derived therapies and vaccines, as well as research in immunomodulation and biologics. The site is home to the Takeda Cell Therapy engine with a state-of-the-art cell therapy manufacturing facility. Furthermore, Takeda signed a 15-year lease for an approximately 600,000 square foot state-of-the-art R&D and office facility under construction in Kendall Square, which Takeda plans to occupy from 2026.

- *Shonan Health Innovation Park*: Located in Fujisawa and Kamakura in Kanagawa Prefecture in Japan, the Shonan Health Innovation Park ("Shonan iPark") was opened in 2018 when Takeda transformed its Shonan Research Center into the first pharma-led science park in Japan by opening its doors to external parties and is the primary location for Takeda's neuroscience research. To attract more diverse partners and to further the success of the Shonan iPark, Takeda transferred ownership rights of Shonan iPark to a trustee in 2020 and transferred operation of Shonan iPark to a company established by Takeda in 2023. Takeda, as a flagship tenant, is committed to invigorating life science research in Japan.

- *San Diego Research and Development Site*: Our R&D site located in San Diego, California in the United States supports R&D in the gastrointestinal and inflammation and neuroscience areas. The San Diego research center operates as a "biotech-like" site and leverages internal capabilities such as structural biology and biophysics to catalyze research internally and externally.

- *Vienna, Austria Research and Development Site*: Our R&D site, located in Vienna, Austria, supports programs in R&D and in PDT. The research center focuses on biologics programs in R&D and contains manufacturing sites for plasma derived products.

The following summarizes our R&D activities within each of our therapeutic and business areas. The therapeutic candidates in our pipeline disclosed within the key therapeutic and business areas below are in various stages of development, and the contents of the pipeline may change as candidates currently under development are removed and new candidates are introduced. Whether the candidates listed below are ever successfully released as products depends on various factors, including the results of pre-clinical and clinical trials, market conditions for various drugs and regulatory approvals. This table primarily shows the indications for which we are actively pursuing regulatory approval and those regulatory approvals granted. We are also conducting additional studies of certain assets to examine their potential for use in further indications and in additional formulations. The listings in the tables below are limited to the U.S., EU, Japan, and China, but we are also conducting development activities in other regions. "Global" refers to U.S., EU, Japan, and China. Modality of our pipeline assets in the following table is classified into either of the following categories: 'small molecule', 'peptide/oligonucleotide', 'cell and gene therapy' or 'biologic and other.'

Gastrointestinal and Inflammation

In Gastrointestinal and Inflammation, Takeda focuses on delivering innovative, life-changing therapeutics for patients with gastrointestinal diseases, including those of the liver as well as other immune-mediated inflammatory diseases. Takeda is maximizing the potential of our inflammatory bowel disease (IBD) franchise around ENTYVIO, including development of a subcutaneous formulation and expansion into other indications such as active chronic pouchitis. Takeda is also expanding its position with GATTEX/REVESTIVE, and ALOFISEL which is currently in Phase 3 trial to support further potential geographic expansion in the U.S. Furthermore, Takeda is progressing a pipeline built through in-house discovery, partnerships and business development, exploring opportunities in inflammatory diseases (IBD, celiac disease, psoriasis, psoriatic arthritis, system lupus erythematosus, others), select liver diseases, and motility disorders. Fazirsiran (TAK-999) is an example of an addition through partnership and a potential first-in-class RNAi for alpha-1 antitrypsin-deficiency associated liver disease in late-stage development. TAK-279 is an example of an acquisition through business development of a late-stage, potential best-in-class oral allosteric tyrosine kinase 2 (TYK2) inhibitor with potential to treat inflammatory diseases.

Note: Therapeutic area name is now "Gastrointestinal and Inflammation" (previously called "Gastroenterology (GI)"), expanding the GI identity, to better reflect our pipeline today and our broad ambition in immune-mediated disease.

Our gastrointestinal and inflammation pipeline in clinical development as of May 11, 2023 (the date of our annual earnings release), along with notes for major subsequent developments thereafter, is as follows:

Development code <generic name> Brand name (country/region)	Type of Drug (administration route)	Modality	Indications / additional formulations	Country/ Region	Stage
MLN0002 <vedolizumab> *ENTYVIO* (Global)	Humanized monoclonal antibody against α4β7 integrin (injection)	Biologic and other	Subcutaneous formulation for ulcerative colitis	Japan U.S.	Approved (Mar 2023) Filed (Apr 2023)
			Subcutaneous formulation for Crohn's disease	Japan U.S.	Filed (Oct 2022) P-III
			Graft-versus-Host Disease prophylaxis in patients undergoing allogeneic hematopoietic stem cell transplantation	EU Japan	P-III P-III
			Pediatrics Study (ulcerative colitis, Crohn's disease)	Global	P-III

TAK-438 <vonoprazan> *TAKECAB* (Japan) *VOCINTI* (China)	Potassium-competitive acid blocker (oral)	Small molecule	Acid related diseases (adjunct to *Helicobacter pylori* eradication)	China	Filed (Aug 2022)
Cx601 <darvadstrocel> *ALOFISEL* (EU, Japan)	A suspension of allogeneic expanded adipose-derived stem cells (injection)	Biologic and other	Refractory complex perianal fistulas in patients with Crohn's disease	U.S.	P-III
			Pediatric indication for refractory complex perianal fistulas in patients with Crohn's disease	EU Japan	P-III P-III
TAK-999(1) <fazirsiran>	GalNAc based RNA interference (RNAi) (injection)	Peptide/ Oligo-nucleotide	Alpha-1 antitrypsin-deficiency associated liver disease	U.S. EU	P-III P-III
TAK-625(2) <maralixibat>	IBAT inhibitor (oral)	Small molecule	Alagille Syndrome	Japan	P-III
			Progressive Familial Intrahepatic Cholestasis	Japan	P-III
TAK-227/ZED1227(3)	Transglutaminase 2 inhibitor (oral)	Small molecule	Celiac disease	-	P-II (b)
TAK-279	TYK2 inhibitor (oral)	Small molecule	Psoriasis	-	P-II (b)
			Psoriatic Arthritis	-	P-II (b)
TAK-062 <zamaglutenase>	Glutenase (oral)	Biologic and other	Celiac disease	-	P-II
TAK-101(4)	Tolerizing Immune Modifying nanoParticle (TIMP) (injection)	Biologic and other	Celiac disease	-	P-II
TAK-951	Peptide agonist (subcutaneous infusion)	Peptide/ Oligo-nucleotide	Nausea and vomiting	-	P-II
TAK-105	Peptide agonist (subcutaneous infusion)	Peptide/ Oligo-nucleotide	Nausea and vomiting	-	P-I
TAK-647	Anti MAdCAM-1 antibody (injection)	Biologic and other	Nonalcoholic Steatohepatitis (NASH)	-	P-I(5)

Notes:
(1) Partnership with Arrowhead Pharmaceuticals, Inc.
(2) Partnership with Mirum Pharmaceuticals.
(3) Partnership with Zedira and Dr. Falk Pharma.
(4) Acquired development and commercialization license for TAK-101 from COUR Pharmaceuticals. Previously known as TIMP-GLIA.
(5) Study actively recruiting.

Neuroscience

In Neuroscience, Takeda is focusing its R&D investments on potentially transformative treatments for neurological and neuromuscular diseases of high unmet need and building its pipeline through a combination of in-house expertise and partnerships. By harnessing advances in disease biology understanding, translational tools, and innovative modalities, Takeda is primarily focusing on rare neurology, in particular, on potential investigative therapies for sleep-wake disorders such as narcolepsy and idiopathic hypersomnia with a franchise of orexin-2 receptor agonists (TAK-861, danavorexton (TAK-925), etc.), rare epilepsies with soticlestat (TAK-935) and central nervous system (CNS) and somatic symptoms of Hunter Syndrome with pabinafusp alfa (TAK-141). Additionally, Takeda makes targeted investments to investigate well-defined segments of neuromuscular diseases, neurodegenerative diseases and movement disorders.

Note: Pabinafusp alfa (TAK-141) and TAK-611 will be developed in Neuroscience starting from FY2023 Q1 and may benefit from Neuroscience's CNS expertise.

Our neuroscience pipeline in clinical development as of May 11, 2023 (the date of our annual earnings release), along with notes for major subsequent developments thereafter, is as follows:

Development code <generic name> Brand name (country/region)	Type of Drug (administration route)	Modality	Indications / additional formulations	Country/ Region	Stage
TAK-935 <soticlestat>	CH24H inhibitor (oral)	Small molecule	Dravet syndrome	Global	P-III
			Lennox-Gastaut syndrome	Global	P-III
TAK-141/JR-141[1] <pabinafusp alfa>	Fusion protein of an antibody against the human transferrin receptor and iduronate-2-sulfatase [recombinant] (injection)	Biologic and other	Hunter syndrome (CNS and somatic symptoms)	EU	P-III
TAK-861	Orexin 2R agonist (oral)	Small molecule	Narcolepsy type 1	-	P-II (b)
			Narcolepsy type 2	-	P-II (b)
TAK-071	M1 positive allosteric modulator (M1PAM) (oral)	Small molecule	Parkinson's disease	-	P-II
TAK-041/NBI-846[2]	GPR139 agonist (oral)	Small molecule	Anhedonia in major depressive disorder (MDD)	-	P-II
TAK-653/NBI-845[2]	AMPA receptor potentiator (oral)	Small molecule	Inadequate response to treatment in major depressive disorder (MDD)	-	P-II
TAK-341/MEDI1341[3]	Alpha-synuclein antibody (injection)	Biologic and other	Multiple systems atrophy (MSA)	-	P-II
TAK-611	Human arylsulfatase A for intrathecal administration [recombinant] (injection)	Biologic and other	Metachromatic leukodystrophy	-	P-II
TAK-594/DNL593[4]	Brain-penetrant progranulin fusion protein (injection)	Biologic and other	Frontotemporal dementia	-	P-II
TAK-925 <danavorexton>	Orexin 2R agonist (injection)	Small molecule	Postanesthesia Recovery, narcolepsy	-	P-I
TAK-920/DNL919[4]	Brain-penetrant TREM2 agonist monoclonal antibody (injection)	Biologic and other	Alzheimer's disease	-	P-I

Notes:
(1) Partnership with JCR Pharma. JCR leads development.
(2) Partnership with Neurocrine Biosciences. Neurocrine leads development.
(3) Partnership with AstraZeneca. P-I Parkinson's disease study is completed.
(4) Partnership with Denali Therapeutics. Denali leads P-I development.

Oncology

In Oncology, we aspire to cure cancer, with inspiration from patients and innovation from everywhere. We are focused on: (1) building on our legacy in hematologic malignancies with marketed products (NINLARO, ADCETRIS, and ICLUSIG, etc.) and pipeline programs; (2) growing a solid tumor portfolio with marketed lung cancer products (ALUNBRIG and EXKIVITY), and development programs in other areas, including colorectal cancer with fruquinitinib (TAK-113); and (3) advancing a cutting-edge pipeline focused on the power of innate immunity.

Our oncology pipeline in clinical development as of May 11, 2023 (the date of our annual earnings release), along with notes for major subsequent developments thereafter, is as follows:

Development code <generic name> Brand name (country/region)	Type of Drug (administration route)	Modality	Indications / additional formulations	Country/ Region	Stage
TAK-788 <mobocertinib> *EXKIVITY* (U.S., China)	EGFR/HER2 exon 20 inhibitor (oral)	Small molecule	Previously treated Non-Small Cell Lung Cancer with EGFR exon 20 insertion[1]	China EU[2] Japan	Approved (Jan 2023) Filing withdrawn (Jul 2022) P-III
			Treatment Naïve Non-Small Cell Lung Cancer with EGFR exon 20 insertion	Global	P-III
TAK-113[3] <fruquintinib>	VEGFR inhibitor (oral)	Small molecule	Metastatic Colorectal Cancer (mCRC)	U.S. EU Japan	Filed (March 2023) P-III P-III
SGN-35[4] <brentuximab vedotin> *ADCETRIS* (EU, Japan, China)	CD30 monoclonal antibody-drug conjugate (injection)	Biologic and other	Relapsed or refractory cutaneous T-cell lymphoma	Japan	Filed (Feb 2023)
			First line Hodgkin's lymphoma – Stage III	EU	Filed (Mar 2023)
MLN9708 <ixazomib> *NINLARO* (Global)	Proteasome inhibitor (oral)	Small molecule	Maintenance therapy in patients with newly diagnosed Multiple Myeloma following autologous stem cell transplant (TOURMALINE-MM3)	U.S. EU	P-III P-III
<cabozantinib>[5] *CABOMETYX* (Japan)	Multi-targeted kinase inhibitor (oral)	Small molecule	Metastatic Castration-Resistant Prostate Cancer in combination with atezolizumab[6]	Japan	P-III
<ponatinib> *ICLUSIG* (U.S.)	BCR-ABL inhibitor (oral)	Small molecule	Front line Philadelphia chromosome-positive Acute Lymphoblastic Leukemia	U.S.	P-III
			Pediatric indication for Philadelphia chromosome-positive Acute Lymphoblastic Leukemia	-	P-I
TAK-385 <relugolix>	LH-RH antagonist (oral)	Small molecule	Prostate cancer	Japan China	P-III P-III
TAK-981 <subasumstat>	SUMO inhibitor (injection)	Small molecule	Multiple cancers	-	P-II
TAK-573[7] <modakafusp alfa>	Anti-CD38-targeted IgG4 genetically fused with an attenuated IFNα (injection)	Biologic and other	Relapsed/refractory Multiple Myeloma	-	P-II
			Solid tumors	-	P-I
TAK-007[8]	CD19 CAR-NK (injection)	Cell and gene therapy	Relapsed/refractory B cell malignancies	-	P-II
TAK-102[9]	GPC3 CAR-T (injection)	Cell and gene therapy	Solid tumors	-	P-I
TAK-103[9]	Mesothelin CAR-T (injection)	Cell and gene therapy	Solid tumors	-	P-I
TAK-676	STING agonist (injection)	Small molecule	Solid tumors	-	P-I

TAK-500	STING agonist antibody drug conjugate (injection)	Biologic and other	Solid tumors	-	P-I
TAK-940[10]	CD19 1XX CAR-T (injection)	Cell and gene therapy	Relapsed/refractory B cell malignancies	-	P-I
TAK-186[11]	T Cell Engager (injection)	Biologic and other	EGFR expressing solid tumors	-	P-I
TAK-280[11]	T Cell Engager (injection)	Biologic and other	B7-H3 expressing solid tumors	-	P-I

Notes:
(1) The U.S. FDA review was conducted under Project Orbis, an initiative of the FDA Oncology Center of Excellence (OCE), which provides a framework for concurrent submission and review of oncology products among international partners. Currently, approval was granted in the U.K. (May 2022), the Switzerland (Jun 2022), Australia (Jul 2022), South Korea (Jul 2022), and Brazil (Mar 2023).
(2) Following discussions with the EMA, Takeda decided to withdraw the marketing authorization application (MAA).
(3) Partnership with HUTCHMED
(4) Partnership with Seagen, Inc.
(5) Partnership with Exelixis, Inc.
(6) Partnership with Chugai Pharmaceutical. Takeda operates P-III development
(7) Partnership with Teva Pharmaceutical Industries Ltd.
(8) Partnership with The University of Texas MD Anderson Cancer Center
(9) Partnership with Noile-Immune Biotech, Inc.
(10) Partnership with Memorial Sloan Kettering Cancer Center
(11) Acquired via acquisition of Maverick Therapeutics, Inc.

Rare Genetics and Hematology

In Rare Genetics and Hematology, Takeda focuses on several areas of high unmet medical need. In hereditary angioedema, Takeda aspires to transform the treatment paradigm, including through TAKHZYRO, with continued investment in lifecycle management programs. In rare hematology, Takeda focuses on addressing today's needs in the treatment of bleeding disorders, including through ADVATE and ADYNOVATE/ ADYNOVI, as well as on the development of pipeline assets including apadamtase alfa/cinaxadamtase alfa (TAK-755) for the treatment of immune thrombotic thrombocytopenic purpura (iTTP) and congenital thrombotic thrombocytopenic purpura (cTTP). In addition, Takeda aims to redefine the management of post-transplant cytomegalovirus (CMV) infection/disease with LIVTENCITY. While we recently decided to discontinue discovery and pre-clinical activities in adeno-associated virus (AAV) gene therapy, Takeda remains committed to fulfilling our vision to deliver life-transforming medicines to patients with rare diseases.

Our rare genetic and hematology pipeline in clinical development as of May 11, 2023 (the date of our annual earnings release), along with notes for major subsequent developments thereafter, is as follows:

Development code <generic name> Brand name (country/region)	**Type of Drug (administration route)**	**Modality**	**Indications / additional formulations**	**Country/ Region**	**Stage**
TAK-620[1] <maribavir> *LIVTENCITY* (U.S., EU)	Benzimidazole riboside inhibitor (oral)	Small molecule	Post-transplant cytomegalovirus (CMV) infection/ disease resistant/refractory to (val) ganciclovir, cidofovir or foscarnet	EU China	Approved (Nov 2022) Filed (Dec 2022)
			Treatment of CMV Infection/disease Post Transplantation (Including HSCT)	Japan	P-III
TAK-743 <lanadelumab> *TAKHZYRO* (Global)	Plasma kallikrein inhibitor (injection)	Biologic and other	Pediatric Hereditary Angioedema	U.S. EU	Approved (Feb 2023) Filed (Dec 2022)
TAK-672[2] *OBIZUR* (U.S., EU)	Porcine Coagulation Factor VIII [recombinant] (injection)	Biologic and other	Acquired hemophilia A (AHA)	China Japan	Filed (Jun 2022) P-II/III

TAK-577 *VONVENDI* (U.S., Japan) *VEYVONDI* (EU)	von Willebrand factor [recombinant] (injection)	Biologic and other	Adult on-demand and surgery treatment of von Willebrand disease	China	Filed (Jan 2023)
			Adult prophylactic treatment of von Willebrand disease	EU China	Filed (Mar 2023) P-III
			Pediatric on-demand and surgery treatment of von Willebrand disease	Global	P-III
TAK-660 *ADYNOVATE* (U.S., Japan) *ADYNOVI* (EU)	Antihemophilic factor [recombinant], PEGylated (injection)	Biologic and other	Pediatric Hemophilia A	EU	P-III
TAK-755[3] <apadamtase alfa/ cinaxadamtase alfa>	Replacement of the deficientADAMTS13 enzyme (injection)	Biologic and other	Congenital Thrombotic Thrombocytopenic Purpura	Global	P-III[5]
			Immune Thrombotic Thrombocytopenic Purpura	U.S. EU	P-II P-II
			Sickle cell disease	U.S.	P-I
TAK-079[4] <mezagitamab>	Anti-CD38 monoclonal antibody (injection)	Biologic and other	Myasthenia gravis	-	P-II
			Immune thrombocytopenic purpura	-	P-II
			Systemic lupus erythematosus	-	P-I/II
			Immunoglobulin A nephropathy	-	P-I

Notes:
(1) Partnership with GlaxoSmithKline.
(2) Partnership with IPSEN.
(3) Partnership with KM Biologics.
(4) Relapsed/refractory Multiple Myeloma will continue until trial completion.
(5) Filed in the U.S. in May 2023.

Plasma-Derived Therapies (PDT)

Takeda has created a dedicated PDT business unit with a focus to manage the business end-to-end, from plasma collection to manufacturing, R&D, and commercialization. In PDT, we aspire to develop life-saving plasma derived treatments which are essential for patients with a variety of rare and complex chronic diseases. The dedicated R&D organization in PDT is charged with maximizing the value of existing therapies, identifying new targeted therapies, and optimizing efficiencies of current product manufacturing. Near-term, our priority is focused on delivering value from our broad immunoglobulin portfolio (HYQVIA, CUVITRU, GAMMAGARD and GAMMAGARD S/D) through pursuit of new indications, geographic expansions, and enhanced patient experience through integrated healthcare technologies. In our hematology and specialty care portfolio, our priority is pursuing new indication and formulation development opportunities for PROTHROMPLEX (4F-PCC), FEIBA, CEPROTIN and ARALAST. Additionally, we are developing next generation immunoglobulin products with 20% fSCIg (TAK-881), IgG Low IgA (TAK-880) and pursuing other early stage opportunities (e.g. hypersialylated Immunoglobulin (hsIgG)) that would add to our diversified commercial portfolio of more than 20 therapeutic products distributed worldwide.

Our PDT pipeline in clinical development as of May 11, 2023 (the date of our annual earnings release), along with notes for major subsequent developments thereafter, is as follows:

Development code <generic name> Brand name (country/region)	Type of Drug (administration route)	Modality	Indications / additional formulations	Country/ Region	Stage
TAK-771[1] <IG Infusion 10% (Human) w/ Recombinant Human Hyaluronidase> *HYQVIA* (U.S., EU)	Immunoglobulin (IgG) + recombinant hyaluronidase replacement therapy (subcutaneous infusion)	Biologic and other	Pediatric indication for primary immunodeficiency	U.S.	Approved (Apr 2023)
			Chronic inflammatory demyelinating polyradiculoneuropathy	U.S. EU	Filed (Feb 2023) Filed (Mar 2023)
			Chronic inflammatory demyelinating polyradiculoneuropathy and Multifocal Motor Neuropathy	Japan	P-III
			Primary Immunodeficiencies	Japan	P-III
TAK-662 *CEPROTIN* (U.S., EU)	Protein C concentrate [human] (injection)	Biologic and other	Long-term prophylaxis treatment of severe congenital protein C deficiency	EU	Approved (Dec 2022)
			Severe congenital protein C deficiency	Japan	Filed (Apr 2023)
TAK-664 <IG Infusion 20% (Human)> *CUVITRU* (U.S., EU)	Immunoglobulin 20% [human] (subcutaneous infusion)	Biologic and other	Primary Immunodeficiencies and Secondary Immunodeficiencies	Japan	Filed (Oct 2022)
TAK-880 <10% IVIG (Low IgA)>	Immunoglobulin (10%) [human] (injection) (Low IgA)	Biologic and other	Primary Immunodeficiencies and Multifocal Motor Neuropathy	U.S. EU	Filed (Jan 2023)[2] Filing in preparation[3]
TAK-330 *PROTHROMPLEX TOTAL* (EU)	Four-factor prothrombin complex concentrate [human] (injection)	Biologic and other	Coagulation Disorder, Direct Oral Anticoagulants (DOAC) reversal in surgical situations	U.S.	P-III
TAK-961 <5% IVIG> *GLOVENIN-I* (Japan)	Immunoglobulin (5%) [human] (injection)	Biologic and other	Autoimmune Encephalitis (AE)	Japan	P-III
TAK-881 <Facilitated 20% SCIG>	Immunoglobulin (20%) [human] + recombinant hyaluronidase replacement therapy (injection)	Biologic and other	Immunodeficiencies	U.S. EU	P-I/II

Notes:
(1) Partnership with Halozyme.
(2) In May 2023, Takeda received a complete response letter (CRL) from FDA regarding its new drug approval application for TAK-880. Takeda is evaluating the CRL and assessing next steps.
(3) Non-interventional study to collect data is in progress.

Vaccines

In Vaccines, Takeda is applying innovation to tackle some of the world's most challenging infectious diseases such as dengue (QDENGA (development code: TAK-003)), COVID-19 (NUVAXOVID), and zika (TAK-426). To support the expansion of our pipeline and the development of our programs, we have entered into partnerships with government organizations in Japan and the U.S., and leading global institutions. Such partnerships have been essential in building the critical capabilities that will be necessary to deliver on our programs and realize their full potential.

Our vaccines pipeline in clinical development as of May 11, 2023 (the date of our annual earnings release), along with notes for major subsequent developments thereafter, is as follows:

Development code Brand name (country/region)	Type of vaccine (administration route)	Modality	Indications / additional formulations	Country/ Region	Stage
TAK-019/ NVX-CoV2373[1] *NUVAXOVID* *Intramuscular Injection* (Japan)	SARS-CoV-2 vaccine (injection)	Biologic and other	Active immunization for the prevention of COVID-19 (primary and booster)	Japan	Approved (Apr 2022)
			Active immunization for the prevention of COVID-19 (heterologous booster)	Japan	P-III
TAK-003[2] *QDENGA* (EU)	Tetravalent dengue vaccine (injection)	Biologic and other	For the prevention of dengue fever of any severity, due to any serotype, in individuals aged 4 and older	EU U.S.	Approved (Dec 2022)[3] Filed (Nov 2022)
			For the prevention of dengue fever of any severity, due to any serotype, in individuals aged 4 and older (booster extension)	-	P-III
TAK-426[4]	Zika vaccine (injection)	Biologic and other	Active immunization for the prevention of disease caused by Zika virus	-	P-I

Notes:
(1) Partnership with Novavax, Inc.
(2) QDENGA (TAK-003) was approved in Indonesia (Aug 2022) and Brazil (Mar 2023).
(3) Takeda participated in the European Medicines Agency's (EMA) parallel assessment of a medicinal product for use in EU, and through the EU-M4all procedure for countries outside of the EU. In October 2022, the Committee for Medicinal Products for Human Use (CHMP) of the EMA recommended the approval of TAK-003 in Europe and in dengue-endemic countries participating in the parallel EU-M4all procedure.
(4) Partnership with The Biomedical Advanced Research and Development Authority (BARDA) of the U.S. Government.

Discontinued projects

Our discontinued projects since April 1, 2022 are as follows:

Development code <generic name>	Indications (Region/Country, Stage)	Reason
<brigatinib>	2L ALK-positive Non-Small Cell Lung Cancer (head-to-head with alectinib) (U.S., EU, P-III)	The study met futility boundary for the primary endpoint.
TAK-994	Narcolepsy (P-II)	TAK-994 was on clinical hold, we have made data driven decision to stop further development and pivot to TAK-861 and other molecules in orexin portfolio like TAK-925.
TAK-039	Clostridium difficile infection (P-I)	Takeda made the strategic decision to discontinue pursuit of TAK-039 in order to further optimize the portfolio.
TAK-605	Solid tumors (P-I)	Takeda has decided to terminate its collaboration with Turnstone Biologics to develop the armored oncolytic virus TAK-605 for strategic reasons and has returned global rights to the asset back to Turnstone. The two companies' discovery efforts to identify additional novel product candidates based on the vaccinia virus platform are ongoing.
TAK-834	Hypoparathyroidism (P-I study in Japan completed)	Japan development was discontinued along with the discontinuation of manufacturing NATPAR/NATPARA globally.
TAK-510	Nausea and vomiting (P-I)	Phase 1 data did not support further development.
<cabozantinib>	2L metastatic Non-Small Cell Lung Cancer in combination with atezolizumab (Japan, P-III)	Phase 3 CONTACT-01 study did not meet its primary endpoint. The result did not support further development in this indication.
TAK-954	Post-operative gastrointestinal dysfunction (P-II(b))	Phase 2 (b) study did not meet its endpoints. Takeda and Theravance Biopharma mutually agreed to discontinue further development of this program and the parties' collaboration agreement.
TAK-018/EB8018 <sibofimloc>	Crohn's disease (post-operative and ileal-dominant) (P-II(a))	Phase 2 (a) study did not meet its endpoints.
MLN9708 <ixazomib>	Maintenance therapy in patients with newly diagnosed Multiple Myeloma not treated with stem cell transplant (TOURMALINE-MM4) (U.S., EU, China, P-III)	While there are ongoing discussions with regulatory bodies around world, given the final analysis of the trial, Takeda will not pursue this indication in the US, EU (NINLARO has been approved in the maintenance setting in Japan, South Korea, Thailand, Taiwan, and Brazil).
TAK-620 <maribavir>	HSCT Recipients with First CMV Infection (U.S., EU, P-III)	After reviewing the study data with regulatory bodies, Takeda decided not to pursue this indication further.
TAK-743 <lanadelumab>	Bradykinin-Mediated Angioedema (Global, P-III)	The Phase 3 study in angioedema patients with normal C1 inhibitor did not meet its primary endpoint. There were no new safety signals and TAKHZYRO's indication for prophylaxis to prevent attacks of Hereditary Angioedema (HAE) remains unchanged.
<niraparib>	Breast cancer (Japan, P-III)	Following GSK's permanent discontinuation of enrolment in the ZEST global Phase 3 study due to eligibility challenges impacting the ability to fully enroll targeted patients, Takeda discontinued enrollment in this study in Japan.

Notes:
Takeda decided to discontinue discovery and pre-clinical efforts in adeno-associated virus (AAV) gene therapy.

Availability of Raw Materials

In the ordinary course of business, we purchase raw materials and supplies essential to our operations from suppliers around the world. While we develop and manufacture the active ingredients used in some of our products at our own facilities, we are dependent on third-party suppliers for a portion of the raw materials and compounds used in certain other products we produce. We believe that, in the event we are unable to source any products or ingredients from any of our major suppliers, we could replace those products or substitute ingredients from other suppliers, although we may not be able to do so without significant difficulty or significant increases in our cost of sales. While efforts are made to diversify our sources of components and materials, in certain instances we acquire components and materials from a sole supplier.

In the case of plasma-derived-therapies, we are dependent on healthy individuals to donate human plasma to develop and manufacture our products. We own and operate plasma donation facilities, principally in the U.S., Austria, Hungary and Czech Republic, and we also maintain relationships with other plasma suppliers for external sourcing to meet our planned supply commitments to patients.

We closely monitor, continuously review and revise the supply sourcing strategy for our products to identify in a timely manner any risks in our supply chain, including risks arising from our dependency on outsourced manufacturing relationships with third party suppliers. Where necessary, inventory levels of either key materials or finished products are managed strategically to address potential risks relating to operational and quality issues, production capacity and single sourcing among others. For critical and strategic products, we have decided to make significant long-term capital investments to build internal manufacturing capacity and secure dual sources to reduce the dependency on outsourced manufacturing relationships with third-party suppliers.

Manufacturing

The manufacturing of our products is highly regulated by governmental health authorities around the world, including the FDA, EMA, Japan's Pharmaceuticals and Medical Devices Agency ("PMDA") and NMPA. Furthermore, many of our products involve technically complex manufacturing processes or may require a supply of highly specialized raw materials.

We manufacture a certain number of our products in our own facilities within our global manufacturing network. In addition, we source certain other products from third-party contract manufacturers. We have a network of over 130 contract manufacturers which provide varying services such as the manufacture of active pharmaceutical ingredients, bulk drug product, aseptic fill finish and final packaging. In cases where we utilize contract manufacturers, we are often dual sourced with an internal manufacturing site. In cases where we are not dual sourced, we manage the risks associated with the reliance on a single source of production by carrying additional inventories.

Sales and Marketing

Our primary sales and marketing activities are organized around regional business units and select therapeutic area business units focused on the U.S., Japan, Europe and Canada, China, and Growth and Emerging Markets. These business units make focused investments that support the growth potential of our portfolios in each market.

The U.S. is the largest pharmaceutical market in the world and is also Takeda's largest region by revenue. The United States Business Unit ("USBU") is focused on the successful uptake of recently approved products such as *LIVTENCITY,* as well as continuing to grow core promoted brands such as *ENTYVIO*, *TRINTELLIX*, *VYVANSE*, *GATTEX, TAKHZYRO* and Immunoglobulin products. These and other principal products are supported by significant investment in marketing and sales force promotion.

The Japan Pharma Business Unit ("JPBU") is focused on retaining Takeda's position as one of the leading pharmaceutical companies in our home market of Japan. Although we continue to promote our strong primary care portfolio, with the Japanese government driving stricter control of drug prices and promoting the penetration of generics, our strategy is to shift focus more towards the uptake of our highly innovative and differentiated specialty medicines such as *ENTYVIO, GATTEX/REVESTIVE* and *ALOFISEL*.

The Europe and Canada ("EUCAN") business unit focuses on a specialized approach in the European and Canadian markets, where public insurance has set a higher bar for the reimbursement of medicines, requiring innovation and clear differentiation in order for products to be reimbursed.

The China Business Unit ("China BU") focuses on unleashing the growth potential in world's second largest pharmaceutical market. The China Business Unit continues to maximize the value of brands like *HUMAN ALUBUMIN/FLEXBUMIN*, *ENANTONE*, *ADVATE*, *NINLARO*, and *VOCINTI* while also aiming to bring other new medicines to China in the future from the therapeutic areas of Gastrointestinal and Inflammation, Neuroscience, Oncology, and Rare Genetics and Hematology.

The Growth and Emerging Markets ("GEM") business unit is focused on delivering highly innovative medicines to patients living with complex and rare diseases in our five key business areas of GI, Rare Diseases, PDT, Oncology and Neuroscience.

The Oncology Business Unit ("OBU") is focused on the development and marketing of oncology medicines in the US, Japan, Europe and Canada. Our promoted oncology portfolio consists of two global brands (*ALUNBRIG* and *EXKIVITY*) as well as products that we market on a regional basis including *ICLUSIG* in the US, *ADCETRIS* in Europe and Japan, and *VECTIBIX*, *ZEJULA*, and *CABOMETYX* in Japan.

The PDT Business Unit is focused on transforming the lives of patients from the collection of plasma to the production and delivery of life-saving medicines worldwide. We offer a broad portfolio of greater than twenty therapies, four of which represent Global Brands for Takeda,

HYQVIA and *CUVITRU*, subcutaneous immunoglobulin, *KIOVIG/GAMMAGARD LIQUID*, intravenous immunoglobulin, and *FLEXBUMIN*, our differentiated bag Albumin product.

The Global Vaccine Business Unit ("VBU") is applying innovation to tackle some of the world's most challenging infectious diseases, such as dengue, Zika, pandemic influenza, and COVID-19 through partnered programs in Japan with Moderna and Novavax.

In 2022, we organized a new division, the Global Portfolio Division ("GPD"), which is focused on accelerating our growth through a global footprint, as well as a diverse portfolio and pipeline of transformational medicines and vaccines. The GPD comprises the China BU, EUCAN, GEM, VBU, the Global Medical and Global Product & Launch Strategy ("GPLS") functions.

Intellectual Property

An important part of our business strategy is to protect our products and technologies using patents and trademarks, to the extent available. We rely on trade secrets, proprietary know-how, technological innovations and contractual arrangements with third parties to maintain and enhance our competitive position. Our commercial success depends, in part, upon our ability to obtain and enforce strong patents, to maintain trade secret protection, to operate without infringing the proprietary rights of others and to comply with the terms of licenses granted to it. Due to the lengthy development periods for new drugs, the high costs of R&D and the small percentage of researched therapeutic candidates that reach the market, the protection of intellectual property plays an important role in the return of investments for R&D of a new drug.

We seek patent protection for proprietary technology whenever possible in the U.S., Japan and major European countries. Where practicable, we seek patent protection in other countries on a selective basis. In all cases, we endeavor to either obtain patent protection itself or support patent applications through licensors. Patents are our primary means of protecting the technologies we use. Patents provide the holder with the right to exclude others from using an invention related to a pharmaceutical product. We use various types of patents to protect our pharmaceutical products, including substance patents, which cover active ingredients, as well as patents covering usage, manufacturing processes and formulation of drugs.

Our low molecule products (small molecules) are mainly protected by substance patents. While the expiration of a substance patent usually results in a loss of market exclusivity for the protected pharmaceutical products, commercial benefits may continue to be protected by non-substance patents such as patents relating to the method of use of such substance, patents relating the manufacturing method of such substance, and patents relating to the new composition or formulation of such substance. The products can be also protected by regulatory data protection under relevant laws in each country even if the substance patent expired. While our biologics can and may be protected by one or more substance patents, certain products may be protected by non-substance patents and/or regulatory data protection. However, for biologics, patent protection may be less important than for traditional pharmaceutical products, as similar products for the same indication and/or biosimilars may be developed and marketed by competitors without infringing on our patents.

In the U.S., patents generally expire 20 years after the filing date of the application, subject to potential patent term adjustments for delays in patent issuance based upon certain delays in prosecution by the U.S. Patent and Trademark Office. A U.S. pharmaceutical patent that claims a product, method of treatment using a product or method of manufacturing a product may also be eligible for a patent term extension based on the time the FDA took to approve the product. This type of extension may only extend the patent term for a maximum of five years and may not extend the patent term beyond fourteen years from regulatory approval. Only one patent may be extended for any product based on FDA delay. In addition to patent exclusivities, the FDA may provide data or market exclusivity for a new chemical entity or an orphan drug, each of which run in parallel to any patent protection. Regulatory data protection or exclusivity prevents a potential generic competitor from relying on clinical trial data that were generated by the sponsor when establishing the safety and efficacy of its competing product for a period of five years for a new chemical entity, or seven years for an orphan drug. Market exclusivity prohibits any marketing of the same drug for the same indication.

In Japan, a patent can be issued for active pharmaceutical ingredients by the Japan Patent Office ("JPO"). Although methods of treatment, such as dosage and administration, are not patentable in Japan, pharmaceutical compositions for a specific dosage or administration method as well as processes to make a pharmaceutical composition are patentable. Patents in Japan generally expire 20 years after the filing date of the patent application. Patents for pharmaceuticals may be extended for up to five years, depending on the amount of time spent for the drug approval process. Japan also has a regulatory data protection system called a re-examination period of eight years for pharmaceuticals that contain new active pharmaceutical ingredients and four years to six years for new combination product and a ten-year orphan drug exclusivity system.

In the EU, patent applications may be filed in the European Patent Office ("EPO") or in a country in Europe. The EPO system permits a single application to be granted for the EU, plus certain other non-EU countries, such as Switzerland and Turkey. When the EPO grants a patent, it is then validated in the countries that the patent owner designates. While the term of a patent granted by the EPO or a European country office may be extended or adjusted, it is generally 20 years from the filing date of the patent application. Pharmaceutical patents covering an approved medicinal product can be granted a further period of exclusivity under the Supplementary Protection Certificate ("SPC") system. SPCs are designed to compensate the owner of the patent for the time it took to receive marketing authorization by the European Medicines Agency or the National Health Authorities. An SPC may be granted to provide, in combination with the patent, up to 15 years of exclusivity from the date of the first European marketing authorization. However, an SPC cannot last longer than five years. The SPC duration can additionally be extended by a further Pediatric Extension of six months if the SPC relates to a medicinal product for children for which data has been submitted according to a Pediatric Investigation Plan ("PIP"). The post-grant phase of patents, including the SPC system, is currently administered on a country-by-country basis under national laws. Therefore, although regulations concerning patents and SPCs have been created at the EPO and EU level, respectively, due to different national implementation they may not always lead to the same result, for example, if challenged in National Courts in the various EU countries. The EU also provides a system of regulatory data exclusivity for authorized human medicines, which runs in parallel to any patent protection. The system

for drugs being approved today is usually referred to as 8+2+1 rule because it provides an initial period of eight years of data exclusivity, during which a competitor cannot rely on the relevant data, a further period of two years of market exclusivity, during which the data can be used to support applications for marketing authorization but the competitive product cannot be launched and a possible one-year extension of the market exclusivity period if, during the initial eight-year data exclusivity period, the sponsor registered a new therapeutic indication for the concerned drug. However, the additional one-year extension is only available if either no therapy exists for the new indication or if the concerned product provides for the new indication a "significant clinical benefit over existing therapies". This system applies both to national and centralized authorizations. The EU also has an orphan drug exclusivity system for medicines similar to the U.S system. If a medicine is designated as an orphan drug, it benefits from ten years of market exclusivity, during which time a similar medicine for the same indication will not receive marketing authorization. Under certain circumstances, this exclusivity can be extended with a two-year Pediatric Extension for completion of a PIP.

Worldwide, we experience challenges in the area of intellectual property from factors such as the penetration of generic versions of our products following the expiry of the relevant patents and the launch by competitors of over-the-counter versions of our products. Our Global General Counsel is responsible for the oversight of our Intellectual Property operations, as well as our legal operations. Our Intellectual Property Department supports our overall corporate strategy by focusing efforts on three main themes:

- maximization of the value of our products and research pipeline and protection of related rights aligned to the strategies of our therapeutic area units;
- facilitation of more dynamic harnessing of external innovation through partner alliance support; and
- securing and protection of intellectual property rights around the world, including in emerging markets.

As infringement of our intellectual property rights poses a risk of loss of expected earnings derived from those rights, we have internal processes in place to manage patents and other intellectual property. This process includes both remaining vigilant against patent infringement by others as well as exercising caution, starting at the R&D stage, to ensure that our products and activities do not violate intellectual property rights held by others.

In the regular course of business, our patents may be challenged by third parties. We are party to litigation or other proceedings relating to intellectual property rights. Details of material ongoing litigation are provided in Note 32 to our audited consolidated financial statements included in this annual report.

The following table describes our outstanding substance patents and the regulatory data protection ("RDP") (U.S. and EU) or re-examination period ("RP") (Japan) for the indicated product by territory and expiry date. The table includes RDP or RP information only if the protection provided by regulatory exclusivity exceeds the patent expiry. Patent term extensions ("PTE"), SPC, and pediatric exclusivity periods ("PEP") are reflected in the expiry dates to the extent they have been granted by the issuing authority. For PTE's, SPC's, and PEP's in which the application is in process but not yet granted, the extended expiry is separately provided.

Our biologic products may face or already face competition from companies who produce similar products for the same indications, and/or biosimilars, regardless of expiry dates below. Certain European patents are the subject of supplemental protection certificates that provide additional protection for the product in certain countries beyond the dates listed in the table.

Our product	Japan expiry dates[1][2]	U.S. expiry dates[1]	EU expiry dates[1]
Gastroenterology (GI):			
ENTYVIO	Patent: - RP: July 2028[2]	Patent: - RDP: May 2026[7]	Patent: - RDP: May 2025[7]
DEXILANT	Not commercialized	Patent: -	Patent: -
PANTOLOC /CONTROLOC (PANTOPRAZOLE)	Not commercialized	Patent: -	Patent: -
TAKECAB[3]	Patent: August 2031	Patent: -[3]	Patent: -[3]
GATTEX/REVESTIVE	Patent: - RP: June 2031[2]	Patent: -[5]	Patent: - RDP: September 2024
PENTASA[4]	Patent: -[4]	Patent: -	Patent: -[4]
LIALDA/MEZAVANT[3]	Patent: -[3]	Patent: -	Patent: -
RESOLOR/MOTEGRITY	Not commercialized	Patent: - RDP: December 2023	Patent: -

Our product	Japan expiry dates[1][2]	U.S. expiry dates[1]	EU expiry dates[1]
ALOFISEL	Patent: - RP: September 2031[2]	Not commercialized	Patent: - RDP: March 2028
Rare Metabolic:			
ELAPRASE [3]	Patent: - [3]	Patent: -	Patent: -
REPLAGAL	Patent: -	Not commercialized	Patent: -
VPRIV	Patent: - RP: July 2024[2]	Patent: -	Patent: -
Rare Hematology:			
ADVATE	Patent: -	Patent: -	Patent: -
ADYNOVATE/ADYNOVI	Patent: January 2026 RP: March 2024[2]	Patent: February 2026 RDP: November 2027	Patent: February 2024 (Extended expiry of February 2029 if SPC granted) RDP: January 2028
FEIBA[6]	Patent: -	Patent: -	Patent: -
HEMOFIL[6]	Not commercialized	Patent: -	Not commercialized
IMMUNATE[6]	Not commercialized	Not commercialized	Patent: -
IMMUNINE[6]	Not commercialized	Not commercialized	Patent: -
VONVENDI	Patent: - RP: March 2030[2]	Patent: December 2030 RDP: December 2027	Patent: - RDP: August 2028
RECOMBINATE	Not commercialized	Patent: -	Not commercialized
Hereditary Angioedema:			
FIRAZYR	Patent: - RP: September 2028[2]	Patent: -	Patent: -
TAKHZYRO	Patent: January 2031 Extended expiry of January 2036 if PTE granted RP: March 2032[2]	Patent: August 2032 RDP: August 2030	Patent: January 2031 (Extended expiry of November 2033 in some countries) RDP: November 2028
CINRYZE[6]	Not commercialized	Patent: -	Patent: -
Rare Diseases - Others:			
LIVTENCITY	Not commercialized	Patent: - RDP: November 2028	Patent: - RDP: November 2032
Plasma-Derived Therapies (PDT) Immunology:			
GAMMAGARD LIQUID[6]	Not commercialized	Patent: -	Patent: -
HYQVIA[6]	Not commercialized	Patent: - RDP: September 2026	Patent: - RDP: May 2024
CUVITRU[6]	Not commercialized	Patent: - RDP: September 2028	Patent: - RDP: July 2027
FLEXBUMIN[6]	Not commercialized	Patent: -	Patent: -
HUMANALBUMIN[6]	Not commercialized	Patent: -	Not commercialized
GLASSIA[6]	Patent: -[4]	Patent: -	Patent: -[4]
ARALAST[6]	Not commercialized	Patent: -	Not commercialized

Our product	Japan expiry dates[1][2]	U.S. expiry dates[1]	EU expiry dates[1]
Oncology:			
VELCADE[3]	Patent: -[3]	Patent: -	Patent: -[3]
LEUPLIN/ENANTONE	Patent: -	Patent: -	Patent: -
NINLARO	Patent: July 2031 RP: March 2027[2]	Patent: November 2029	Patent: November 2031 RDP: November 2026
ADCETRIS[4]	Patent: July 2028 RP: May 2028[2]	Patent: -[4]	Patent: October 2027 RDP: October 2023
ICLUSIG[3]	Patent: -[3]	Patent: January 2027	Patent: -[3]
ALUNBRIG	Patent: November 2032 RP: January 2029	Patent: April 2031 RDP: April 2024	Patent: May 2029 Extended expiry of November 2033 if SPC granted RDP: November 2028
VECTIBIX[4]	Patent: -	Patent: -[4]	Patent: -[4]
EXKIVITY	Not commercialized	Patent: May 2035 Extended expiry of September 2035 if PTE granted RDP: September 2028	Not commercialized
ZEJULA	Patent: January 2033 RP: September 2028[2]	Patent: -[4]	Patent: -[4]
CABOMETYX[4]	Patent: September 2029 RP: March 2028[2]	Patent: -[4]	Patent: -[4]
Neuroscience:			
VYVANSE/ELVANSE	Patent: June 2029 RP: March 2027[2]	Patent: August 2023	Patent: June 2024 (Extended expiry of February 2028 or March 2029 in certain countries)
TRINTELLIX[4]	Patent: October 2027 RP: September 2027[2]	Patent: June 2026 Extended expiry of December 2026 if pediatric exclusivity (PED) granted	Patent: -[4]
ADDERALL XR	Not commercialized	Patent: -	Not commercialized
ROZEREM	Patent: -	Patent: -	Not commercialized
INTUNIV	Patent: - RP: March 2025[2]	Patent: -	Patent: - RDP: September 2025
Other:			
AZILVA-F	Patent: -	Not commercialized	Not commercialized
LOTRIGA[4]	Patent: -	Patent: -[4]	Patent: -[4]
FOSRENOL	Patent: -[3]	Patent: -	Not commercialized
QDENGA	Not commercialized	Not commercialized	Patent: - RDP: December 2032

Notes:

(1) A "-" within the table indicates the substance patent is expired or not applicable.

(2) In Japan, an application for a generic product is filed after the re-examination period ends, and the product is listed in the approval and drug price listing after a regulatory review. Therefore, the generic product would enter the market after a certain period of time from the expiry of the re-examination period.

(3) This product is not sold by Takeda in all regions because of out-licensing agreements to third parties.

(4) This product is not sold by Takeda in all regions because of in-licensing agreements from third parties exclusive to certain regions. See "—Licensing and Collaboration" for further information on the licensing agreements.

(5) No generic has been launched as of March 2023. The exact timing of the market entry of the generic version of *GATTEX/REVESTIVE* is uncertain.

(6) Relates to plasma-derived therapies products.

(7) Takeda has been granted patents that cover various aspects of *ENTYVIO*, including formulation, dosing regimens and process for manufacturing, some of which are expected to expire in 2032. Any biosimilar that seeks to launch prior to 2032 would need to address potential infringement and/or the validity of all relevant patents and therefore the exact timing of biosimilar entry is uncertain.

Licensing and Collaboration

In the ordinary course of business, we enter into arrangements for licensing and collaboration for the development and commercialization of products with third parties. Our business does not materially depend on any one of these arrangements. Instead they form a portion of our strategy and give us the ability to leverage a mix of internal and external resources to develop and commercialize new products. A sample of the agreements which have led to successful commercialization to date are summarized below:

- *ADCETRIS*: We entered into a Collaboration Agreement with Seagen Inc. (formerly Seattle Genetics, Inc.) ("Seagen") in 2009 for the global co-development of *ADCETRIS* and its commercialization around the world (other than the U.S. and Canada, where ADCETRIS is commercialized by Seagen). We are required to pay milestone payments related to regulatory progress and were required to pay milestone payments related to commercial progress by us under the collaboration. We also pay tiered royalties with percentages ranging from the mid-teens to the mid-twenties based on net sales of *ADCETRIS* within our licensed territories. We and Seagen equally co-fund the cost of selected development activities conducted under the collaboration, but as of March 31, 2023, there are no further incremental potential commercial milestone payments remaining under the ADCETRIS collaboration. Either party may terminate the collaboration for cause, or by mutual consent. We may terminate the collaboration at will, and Seagen may terminate the collaboration in certain circumstances. If neither party terminates the collaboration agreement, then the agreement automatically terminates on the expiration of all payment obligations. In March 2023, Seagen announced that it had entered into a definitive merger agreement with Pfizer Inc. ("Pfizer") and a subsidiary of Pfizer, whereby Seagen will become a wholly-owned subsidiary of Pfizer, following closing of the transaction, which is subject to customary closing conditions.
- *TRINTELLIX:* We entered into a License, Development, Supply and Commercialization Agreement with H. Lundbeck A/S in 2007 for the exclusive co-development and co-commercialization in the U.S. and Japan of several compounds in Lundbeck's pipeline for the treatment of mood and anxiety disorders. Under the agreement, both partners commercialize TRINTELLIX in the U.S. and Japan and have agreed to jointly develop the relevant compounds, with most of development funding provided by us. Revenues for *TRINTELLIX* are booked by us, and we pay Lundbeck a portion of net sales, as well as tiered royalties ranging from the low to mid-teens on the portion of sales retained by us. We have also agreed to pay Lundbeck certain development and commercialization milestone payments relating to regulatory and commercial progress under the collaboration, but as of March 31, 2023, there are no further incremental potential commercial milestone payments remaining under the TRINTELLIX collaboration. The term of the agreement is indefinite, but the agreement may be terminated by mutual decision of the parties or for cause.

The following tables describe other research & development collaborations/partnering and externalization projects entered into by Takeda, but do not represent a comprehensive list of all Takeda R&D collaborations. All of the "subject" descriptions listed below are as of the date of execution of the relevant agreement unless otherwise noted:

Gastrointestinal and Inflammation

Partner	Country of incorporation	Subject
Arrowhead Pharmaceuticals	U.S.	Collaboration and licensing agreement to develop fazirsiran (TAK-999; ARO-AAT), an investigational RNA interference (RNAi) therapy in development to treat alpha-1 antitrypsin-associated liver disease (AATLD). ARO-AAT is a potential first-in-class therapy designed to reduce the production of mutant alpha-1 antitrypsin protein, the cause of AATLD progression.
Cerevance	U.S.	Multi-year research alliance to identify novel target proteins expressed in the central nervous system and to develop new therapies against them for certain GI disorders. Goal of the collaboration is to select, confirm and validate targets from gene expression data sets generated by Cerevance's NETSseq technology.
COUR Pharmaceuticals	U.S.	Takeda has acquired an exclusive global license to develop and commercialize the investigational medicine TIMP-GLIA (TAK-101), an immune modifying nanoparticle containing gliadin proteins.
Engitix	U.K.	Collaboration and licensing agreement to utilize Engitix's unique extracellular matrix discovery platform to identify and develop novel therapeutics for liver fibrosis and fibrostenotic inflammatory bowel disease, including Crohn's disease and ulcerative colitis.
Genevant Sciences Corporation	U.S.	Collaboration and License Agreements to leverage Genevant's hepatic stellate cell-partitioning LNP platform to deliver Takeda-designed RNAi oligonucleotides intended to halt or reverse the progression of liver fibrosis, and to deliver Takeda-designed non-viral gene therapies for the treatment of specified rare liver diseases.
Mirum Pharmaceuticals	U.S.	Exclusive licensing agreement for the development and commercialization of maralixibat (TAK-625) in Japan for Alagille syndrome (ALGS), progressive familial intrahepatic cholestasis (PFIC), and biliary atresia (BA).
Sosei Heptares	U.K.	Collaboration and License agreement to leverage Sosei Heptares's StaR® technology and structural biology expertise with GPCRs to enable structure based drug discovery to advance novel therapeutics for gastroenterology diseases.

UCSD/Fortis Advisors	U.S.	Technology license for the development of oral budesonide formulation (TAK-721) for treatment of eosinophilic esophagitis.
Zedira/Dr. Falk Pharma	Germany	Collaboration and license agreement to develop and commercialize a potential first-in-class therapy TAK-227/ZED1227, a tissue transglutaminase 2 (TG2) inhibitor, designed to prevent the immune response to gluten in celiac disease. Takeda has exclusive rights in the US and other territories outside of Europe, Canada, Australia and China.

Neuroscience

Partner	Country of incorporation	Subject
Anima Biotech	U.S.	Strategic collaboration to discover and develop mRNA translation modulators for genetically-defined neurological diseases.
AstraZeneca	U.K.	Agreement for the joint development and commercialization of MEDI1341/TAK-341, an alpha-synuclein antibody currently in development as a potential treatment for Multiple system atrophy (MSA) and Parkinson's disease.
BioMarin	U.S.	Agreement for the in-license of enabling technology for the exogenous replacement of Arylsulfatase A enzyme with intrathecal (IT) administration directly into the central nervous system for the long-term treatment of patients with metachromatic leukodystrophy (MLD), a rapidly-progressive and ultimately fatal neuro-degenerative rare disease (TAK-611).
BridGene Biosciences	U.S.	Research collaboration to discover small molecule drugs for "undruggable" targets using BridGene's chemoproteomics platform.
CNDAP (Cure Network Dolby Acceleration Partners)	U.S.	Research collaboration to develop small molecules targeting tau, a protein involved in Alzheimer's disease and other major brain disorders.
Denali Therapeutics	U.S.	Strategic option and collaboration agreement to develop and commercialize up to three specified therapeutic product candidates for neurodegenerative diseases, incorporating Denali's transport vehicle (TV) platform for increased exposure of biotherapeutic products in the brain; options exercised on DNL593/TAK-594 and DNL919/TAK-920 in Q3 FY2021.
JCR Pharmaceuticals	Japan	Exclusive collaboration and license agreement to commercialize TAK-141 (JR-141, pabinafusp alfa), applied with J-Brain Cargo®, JCR's proprietary blood-brain barrier (BBB) penetration technology, for the treatment of Hunter syndrome (MPS II). Takeda will exclusively commercialize TAK-141 outside of the United States, including Canada, Europe, and other regions (excluding Japan and certain other Asia-Pacific countries). Takeda receives an option under a separate option agreement, which allows Takeda to acquire an exclusive license to commercialize TAK-141 in the U.S. upon completion of the Phase 3 program. In March 2022, Takeda and JCR entered into a new exclusive license and collaboration agreement to develop gene therapies that apply J-Brain Cargo® BBB penetration technology for lysosomal storage disorders (LSDs); Takeda has the option to nominate additional rare disease and other disease indications.
Luxna Biotech	Japan	Exclusive worldwide license agreement for the use of Luxna's breakthrough xeno nucleic acid technology for multiple undisclosed target genes in the area of neurological diseases.
Neurocrine Biosciences	U.S.	Collaboration to develop and commercialize 7 compounds in Takeda's early-to-mid stage neuroscience pipeline, including TAK-041/NBI-846, TAK-653/NBI-845 and TAK-831/NBI-844 (luvadaxistat). Takeda will be entitled to certain development milestones, commercial milestones and royalties on net sales and will, at certain development events, be able opt in or out of a 50:50 profit share on all clinical programs on an asset-by-asset basis. In June 2021, Takeda decided not to cost share further TAK-831/NBI-844 (luvadaxistat) development; Takeda maintains its right to receive milestones and royalties regarding TAK-831/NBI-844 (luvadaxistat).
PeptiDream	Japan	Collaborative research and exclusive license agreement to create peptide-drug conjugates (PDCs) for neuromuscular and neurodegenerative diseases.
Wave Life Sciences	Singapore	Multi-program option agreement to co-develop and co-commercialize antisense oligonucleotides for a range of neurological diseases.

Oncology

Partner	Country of incorporation	Subject
Adimab	U.S.	Agreement for the discovery, development and commercialization of three mAbs and three CD3 Bi-Specific antibodies for oncology indications.
Crescendo Biologics	U.K.	Collaboration and licensing agreement for the discovery, development and commercialization of Humabody®-based therapeutics for cancer indications.
Egle Therapeutics	France	Identify novel tumor-specific regulatory T cell targets and develop unique anti-suppressor-based immunotherapies.
Exelixis, Inc.	U.S.	Exclusive licensing agreement to commercialize and develop novel cancer therapy cabozantinib and all potential future cabozantinib indications in Japan, including advanced renal cell carcinoma and hepatocellular carcinoma.
GlaxoSmithKline	U.K.	Exclusive licensing agreement to develop and commercialize novel cancer therapy niraparib for the treatment of all tumor types in Japan, and all tumor types excluding prostate cancer in South Korea and Taiwan.
Heidelberg Pharma	Germany	Antibody-Drug-Conjugate (ADC) research collaboration on 2 targets and licensing agreement (α-amanitin payload and proprietary linker).
HUTCHMED	China	Exclusive licensing agreement with HUTCHMED (China) Limited and its subsidiary HUTCHMED Limited for the further development and commercialization of fruquintinib (TAK-113) in all indications, including metastatic colorectal cancer, outside of mainland China, Hong Kong and Macau.
KSQ Therapeutics	U.S.	Strategic collaboration to research, develop and commercialize novel immune-based therapies for cancer using KSQ's CRISPRomics® technology.
MD Anderson Cancer Center (MDACC)	U.S.	Exclusive license and research agreement to utilize MDACC's platform and expertise, and to leverage Takeda's development, manufacturing and commercialization capabilities to bring patients cord blood-derived chimeric antigen receptor-directed natural killer (CAR-NK) cell therapies for the treatment of B cell malignancies and other cancers.
Memorial Sloan Kettering Cancer Center	U.S.	Strategic research collaboration and license to develop novel chimeric antigen receptor T cell (CAR-T) products for the treatment of multiple myeloma, acute myeloid leukemia and additional solid tumor indications. The collaboration is co-led by Michel Sadelain, who is currently head of the Center for Cell Engineering at Memorial Sloan Kettering
National Cancer Center of Japan	Japan	Partnership agreement to develop basic research to clinical development by promoting exchanges among researchers, physicians, and others engaged in anti-cancer drug discovery and cancer biology research.
Noile-Immune Biotech	Japan	Collaboration agreement for the development of next generation CAR-T cell therapy, developed by Professor Koji Tamada at Yamaguchi University. Takeda has exclusive options to obtain licensing rights for the development and commercialization of Noile-Immune Biotech's pipeline and products resulting from this partnership. Due to the success of the collaboration, Takeda licensed NIB-102 and NIB-103.
Presage Biosciences	U.S.	Research collaboration and license for multiple programs using Presage's proprietary platform CIVO (Comparative In Vivo Oncology) to evaluate patients' unique responses to microdoses of cancer drugs.
Teva Pharmaceutical Industries	Israel	Agreement for worldwide license to TEV-48573/TAK-573 (modakafusp alfa, Anti-CD38-Attenukine™) and multi-target discovery collaboration accessing Teva's Attenukine™ platform.
Turnstone Biologics	U.S.	Collaboration to conduct collaborative discovery efforts to identify additional novel product candidates based on a Turnstone's vaccinia virus platform. Takeda has decided to terminate its collaboration to develop the armored oncolytic virus TAK-605 for strategic reasons and has returned global rights to the asset back to Turnstone (FY2022).

Rare Genetics and Hematology

Partner	Country of incorporation	Subject
Asklepios Biopharmaceuticals	U.S.	Agreement for multiple research and development collaborations using FVIII Gene Therapy for the treatment of Hemophilia A and B.
Code Bio	U.S.	Collaboration and license agreement for Takeda and Code Bio to design and develop a targeted gene therapy leveraging Code Bio's 3DNA platform for a liver-directed rare disease program, plus conduct additional studies for central nervous system-directed rare disease programs. Takeda has the right to exercise options for an exclusive license for four programs.
Codexis, Inc.	U.S.	Strategic collaboration and license for the research and development of novel gene therapies for certain disease indications, including the treatment of lysosomal storage disorders and blood factor deficiencies.
Ensoma	U.S.	Research collaboration and license provides Takeda with an exclusive worldwide license to Ensoma's Engenious™ vectors for up to five rare disease indication.
Evozyne	U.S.	Research collaboration and license agreement with Takeda to research and develop proteins that could be incorporated into next-generation gene therapies for up to four rare disease targets.
GlaxoSmithKline	U.K.	In-license agreement between GSK and University of Michigan for TAK-620 (maribavir) in the treatment of human cytomegalovirus.
Immusoft	U.S.	Research collaboration and license option agreement to discover, develop and commercialize cell therapies in rare inherited metabolic disorders with central nervous system (CNS) manifestations and complications using Immusoft's Immune System Programming (ISP™) technology platform.
IPSEN	France	Purchase agreement for the development of OBIZUR for the treatment of Acquired Hemophilia A including for patients with Congenital Hemophilia A with inhibitors indication in elective or emergency surgery.
KM Biologics	Japan	Collaboration and license agreement for the development of therapeutic uses of rADAMTS13 (TAK-755), including but not limited to TTP.
Poseida Therapeutics (1)	U.S.	Research collaboration and exclusive license agreement to utilize Poseida's piggyBac, Cas-CLOVER, biodegradable DNA and RNA nanoparticle delivery technology and other proprietary genetic engineering platforms for up to eight gene therapies.
Selecta Biosciences (2)	U.S.	Research collaboration and license agreement to develop targeted, next-generation gene therapies for two indications within the field of lysosomal storage disorders using Selecta's ImmTOR platform.
Xenetic Biosciences	U.S.	Exclusive R&D license agreement for PolyXen delivery technology for hemophilia factors VII, VIII, IX, X.

Note:

(1) Takeda notified Poseida Therapeutics of its intention to terminate the research collaboration and license agreement effective July 30, 2023.

(2) Takeda notified Selecta Biosciences of its intention to terminate the research collaboration and license agreement effective July 25, 2023.

Plasma Derived Therapies

Partner	Country of incorporation	Subject
Halozyme	U.S.	Agreement for the in-license of Halozyme's proprietary ENHANZE™ platform technology to increase dispersion and absorption of HYQVIA.
Kamada	Israel	In-license agreement to develop and commercialize IV Alpha-1 proteinase inhibitor (GLASSIA); Exclusive supply and distribution of GLASSIA in the U.S., Canada, Australia and New Zealand; work on post market commitments ongoing.
Johnson & Johnson/Momenta Pharmaceuticals	U.S.	In-licensing agreement with Momenta Pharmaceuticals, Inc. which was acquired by Johnson & Johnson for an investigational hypersialylated immunoglobulin (hsIgG) candidate.
PreviPharma	EU	Research collaboration and option agreement to develop new targeted proteins

Vaccines

Partner	Country of incorporation	Subject
U.S. Government - The Biomedical Advanced Research and Development Authority (BARDA)	U.S.	Partnership to develop TAK-426, a Zika vaccine candidate, for the U.S. with the option to use data generated for filing also in affected regions around the world.
Novavax	U.S.	Partnership for the development, manufacturing and commercialization of Nuvaxovid Intramuscular Injection, Novavax' COVID-19 vaccine in Japan, which is being funded by the Government of Japan's Ministry of Health, Labour and Welfare.(MHLW) and Agency for Medical Research and Development (AMED) Takeda finalized an agreement with the MHLW to supply 150 million doses of Nuvaxovid, the supply of which will be dependent on many factors, including need. In February 2023, MHLW cancelled the order of the remaining doses not yet supplied. Takeda is working with Novavax to develop vaccines against the future variants including the Omicron variant.
Moderna	U.S.	Three-way agreement with Moderna and the Government of Japan's Ministry of Health Labour & Welfare (MHLW) to import and distribute Moderna's COVID-19 vaccine, known as Spikevax Intermuscular Injection in Japan. The MHLW granted special approval for the primary series in May 2021 and regulatory approval for a 50 µg booster dose in December 2021. Takeda started importation of 93 million doses (50 µg booster dose) to Japan in 2022, in addition to the 50 million doses (100 µg) delivered in 2021. As of August 2022, Moderna assumed responsibility for all Spikevax™ activities, including import, local regulatory, development, quality assurance and commercialization. Takeda will continue to provide distribution support under the current national vaccination campaign for Moderna COVID-19 vaccines for a transitional period. Both companies will be responsible for ensuring proper implementation of operations associated with this transfer.

Other / Multiple Therapeutic Area

Partner	Country of incorporation	Subject
Bridge Medicines	U.S.	Partnership with Tri-Institutional Therapeutics Discovery Institute, Bay City Capital and Deerfield Management in the establishment of Bridge Medicines. Bridge Medicines will give financial, operational and managerial support to move projects seamlessly from a validating, proof-of-concept study to an in-human clinical trial.
Center for iPS Cell Research Application, Kyoto University (CiRA)	Japan	Collaboration agreement for clinical applications of iPS cells in Takeda strategic areas including applications in neuroscience, oncology and gastroenterology as well as discovery efforts in additional areas of compelling iPSC translational science.
Charles River Laboratories	U.S.	Collaboration on multiple integrated programs across Takeda's core therapeutic areas using Charles River Laboratories' end-to-end drug discovery and safety assessment platform to progress these programs towards candidate status.
Evotec SE	Germany	Research alliance to support Takeda's growing number of research stage gene therapy discovery programs. Evotec and Takeda have also entered into a multi-RNA target alliance to discover and develop RNA targeting small molecule therapeutics for targets that are difficult to address via more conventional approaches.
Massachusetts Institute of Technology	U.S.	MIT-Takeda Program to fuel the development and application of artificial intelligence (AI) capabilities to benefit human health and drug development. Centered within the Abdul Latif Jameel Clinic for Machine Learning in Health (J-Clinic), the new program will leverage the combined expertise of both organizations, and is supported by Takeda's investment.
Schrödinger	U.S.	Agreement for the multi-target research collaboration combining Schrödinger's in silico platform-driven drug discovery capabilities with Takeda's deep therapeutic area knowledge and expertise in structural biology.
Stanford University	U.S.	Collaboration agreement with Stanford University to form the Stanford Alliance for Innovative Medicines to more effectively develop innovative treatments and therapies.
Tri-Institutional Therapeutics Discovery Institute (Tri-I TDI)	U.S.	Agreement for the collaboration of academic institutions and industry to more effectively develop innovative treatments and therapies.
Twist Bioscience	U.S.	Agreement and license for Takeda to access Twist's "Library of Libraries," a panel of synthetic antibody phage display libraries derived only from sequences that exist in the human body. Together, the companies will work to discover, validate and optimize new antibody candidates.

Competition

Competition in each market where we conduct business is based on, among other things, product safety, efficacy, convenience of dosing, reliability, availability and pricing. Our competitors include large international companies whose capabilities cover the entire product creation process from R&D to manufacturing and marketing, as well as biopharmaceutical companies with a focus on specific therapeutic areas.

We also face competition from generic drugs and biosimilars that enter the market when our patent protection or regulatory exclusivity expires. See "*—Intellectual Property*" for additional description of our patents. Additionally, we may face competition from the introduction of our own new products that treat similar diseases as our older products.

The competition we face often differs by product and geographic market, and competitors may emerge and fall away over time due to advances in innovation, merger activity and other business and market changes.

The following table shows the principal sources of competition for our main products:

Our product	Principal competing product	Primary manufacturer or distributor
GI:		
DEXILANT, PANTOPRAZOLE (Protonix)	generic lansoprazole, esomeprazole	—
ENTYVIO	*Remicade*	Janssen Biotech
	Humira	Abbvie
	Stelara	Janssen Biotech
	Xeljanz	Pfizer
	Infliximab biosimilars	Amgen, Pfizer, Organon
	Adalimumab biosimilars	Various
	Rinvoq	AbbVie
	Skyrizi	AbbVie
	Zeposia	BMS
	Jyseleca	Galapagos / Gilead
	Carogra	EA Pharma
TAKECAB	*Nexium*	AstraZeneca
	generic lansoprazole, omeprazole, esomeprazole	—
GATTEX/REVESTIVE	—	—
ALOFISEL	*Autologous tissue, chronic seton usage*	—
	Remicade	Janssen Biotech
	Infliximab biosimilars	Amgen, Pfizer, Organon
Rare Diseases:		
ADVATE and ADYNOVATE	*Xyntha/Refacto AF*	Pfizer and Sobi
	Kogenate	Bayer
	Kovaltry	Bayer
	Eloctate/Elocta	Sanofi and Sobi
	Novoeight	Novo Nordisk
	Nuwiq	Octapharma
	Afstyla	CSL
	Jivi	Bayer
	Esperoct	Novo Nordisk
	Hemlibra	Roche
	Roctavian	Biomarin
	Altuviiio	Sanofi and Sobi
FEIBA	*Hemlibra*	Roche
	Novo 7	Novo Nordisk

Our product	Principal competing product	Primary manufacturer or distributor
TAKHZYRO	*Ruconest*	Pharming
	Generic Icatibant	Various
	Haegarda	CSL
	Berinert	CSL
	Orladeyo	BioCryst
	Androgens	Various
REPLAGAL	*Fabrazyme*	Sanofi Genzyme
	Galafold	Amicus
	Fabagal	Isu Abxis
VPRIV	*Cerezyme*	Sanofi Genzyme
	Elelyso/uplyso	Pfizer/Protalix
	Zavesca	Actelion [Janssen]
	Cerdelga	Sanofi Genzyme
	Abcertin	Isu Abxis
ELAPRASE	*Hunterase*	Korean Green Cross
	IZCARGO	JCR Pharmaceuticals
LIVTENCITY	*Ganciclovir*	Various
	Valganciclovir	Various
	Valaciclovir	Various
	Aciclovir	Various
	Foscarnet	Various
PDT		
GAMMAGARD LIQUID/KIOVIG, GAMMAGARD S/D	*Privigen*	CSL
	Gamunex-C	Grifols
	Flebogamma	Grifols
	Asceniv	ADMA
	Bivigam	ADMA
	Gammaked	Kedrion
	Gammaplex	BPL
	Octagam	Octapharma
	Panzyga	Octapharma
GAMMAGARD LIQUID, HYQVIA, CUVITRU	*Hizentra*	CSL
	Xembify	Grifols
	Gamunex-C	Grifols
	Cutaquig/Gammanorm	Octapharma
FLEXBUMIN and HUMAN ALBUMIN	*Alburex/AlbuRx*	CSL
	Albuminar, Albumex	CSL
	Plasbumin	Grifols
	Albutein/Albutein Flexbag	Grifols
	Albunorm	Octapharma
	Kedbumin, Albuked	Kedrion
Oncology:		
ADCETRIS	*Keytruda*	Merck/MSD
	Opdivo	Bristol-Myers Squibb
ALUNBRIG	*Xalkori*	Pfizer
	Zykadia	Novartis
	Alecensa	Roche
	Lorbrena	Pfizer
ICLUSIG	*Gleevec*	Novartis
	Tasigna	Novartis
	Sprycel	Bristol-Myers Squibb
	Bosulif	Pfizer

Our product	Principal competing product	Primary manufacturer or distributor
LEUPRORELIN (LEUPLIN)	*Zoladex*	AstraZeneca
	generic leuprorelin	—
NINLARO, VELCADE	*Revlimid*	Bristol-Myers Squibb
	Pomalyst/Imnovid	Bristol-Myers Squibb
	Kyprolis	Amgen
	Darzalex	Janssen Biotech
	Empliciti	Bristol-Myers Squibb
	Xpovio	Karyopharm
	Sarclisa	Sanofi
	Papexto	Oncopeptide
	Abecma	Bristol-Myers Squibb
EXKIVITY	*Rybrevant*	Janssen Oncology
Neuroscience:		
TRINTELLIX	*Viibryd*	AbbVie
	Fetzima	AbbVie
	Generics: Amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, desvenlafaxine, doxepin, duloxetine, esketamine, escitalopram, fluoxetine, fluvoxamine, imipramine, maprotiline, mirtazapine, nefazodone, nomifensine, nortriptyline, nefazodone, paroxetine, protriptyline, sertraline, trazodone, trimipramine, venlafaxine	Various
VYVANSE	generic mixed salts of a single-entity amphetamine product:	
	– Adderall IR	Various
	generic mixed salts of a single-entity amphetamine product, extended release:	
	– Adderall XR	Various
	– Dyanavel XR	Tris Pharma
	– Azstarys	Corium
	generic methylphenidate, extended release:	
	– Concerta	Various
	– Jornay PM	Ironshore Pharmaceuticals
	– Adhansia XR	Adlon Therapeutics
	– Quillivant XR	Tris Pharma
	Non-stimulants:	
	– Strattera (atomoxetine)	Various
	– Intuniv (guanfacine)	
	– Kapvay (clonidine)	
	– Qelbree (viloxazine)	Supernus
Other:		
AZILVA	generic candesartan, olmesartan	—

Regulation

The pharmaceutical industry is subject to extensive global regulation by regional, national, state and local agencies. The regulatory agencies govern the testing, approval, production, labeling, distribution, post-market surveillance, advertising, dissemination of information and promotion of our products. The following is a description of the major regulations affecting our products in the U.S., Japan and the EU, our largest markets.

The introduction of new pharmaceutical products generally entails a lengthy approval process. Products must be authorized or registered prior to marketing, and such authorization or registration must subsequently be maintained. In recent years, the registration process has required increased testing and documentation for the approval of new drugs, with a corresponding increase in the expense of introducing a new product to market. To register a pharmaceutical product, a registration dossier containing evidence establishing the safety, efficacy and quality of the product must be submitted to regulatory authorities. Generally, a therapeutic product must be registered in each country in which it will be sold. It is possible that a drug can be registered and marketed in one country while the registration authority in another country may, prior to registration, request additional information from the pharmaceutical company or even reject the product. It is also possible that a drug may be approved for different indications in different countries. The registration process generally takes between six months to several years, depending on the country, the quality of the data submitted, the efficiency of the registration authority's procedures and the nature of the product. Many countries provide for accelerated processing of registration applications for innovative products of therapeutic interest. In recent years, efforts have been made among the U.S., Japan and the EU to harmonize registration requirements to achieve shorter development and registration times for medical products.

United States

In the U.S., applications for drug registration are submitted to and reviewed by the FDA, which regulates the testing, manufacturing, labeling and approval for marketing of pharmaceutical products intended for commercialization. The FDA continues to monitor the safety of pharmaceutical products after they have been approved for sale in the U.S. market. When a pharmaceutical company has gathered data to demonstrate a drug's safety, efficacy and quality, it may file for the drug an NDA or Biologics License Application ("BLA"), along with information regarding the clinical experiences of patients tested in the drug's clinical trials. A supplemental New Drug Application ("sNDA") or supplemental Biologics License Application ("sBLA") must be filed for new indications for a previously approved drug.

Once an application is submitted, the FDA assigns reviewers from its staff, including experts in biopharmaceutics, chemistry, clinical microbiology, pharmacology/toxicology, and statistics. After a complete review, these content experts then provide written evaluations of the NDA or BLA. These evaluations are consolidated and are used by senior FDA staff in its final evaluation of the NDA or BLA. Based on that final evaluation, the FDA then provides to the NDA or BLA's sponsor an approval, or a "complete response" letter if the NDA or BLA application is not approved. If not approved, the letter will state the specific deficiencies in the NDA or BLA which need to be addressed. The sponsor must then submit an adequate response to the deficiencies to restart the review procedure. Once the FDA has approved an NDA, BLA, sNDA or sBLA amendment, the company can make the new drug available for physicians to prescribe. The drug owner must submit periodic reports to the FDA, including any cases of adverse reactions. For some medications, the FDA requires additional post-approval studies (Phase IV) to evaluate long-term effects or to gather information on the use of the product under specified conditions. Throughout the life cycle of a product, the FDA requires compliance with standards relating to good laboratory, clinical and manufacturing practices. The FDA also requires compliance with rules pertaining to the manner in which we may promote our products.

The Drug Price Competition and Patent Restoration Term Act of 1984, known as the Hatch-Waxman Act, established the application procedures for obtaining FDA approval for generic forms of brand-name drugs. Under these procedures, instead of conducting full-scale pre-clinical and clinical trials, the FDA can accept data establishing that the drug formulation, which is the subject of an abbreviated application, is bio-equivalent and has the same therapeutic effect as the previously approved drug, among other requirements. This act also provides market exclusivity provisions for brand-name drugs that can delay the submission and/or the approval of Abbreviated New Drug Applications ("ANDAs"), which are the applications for generic drug registrations. The Orphan Drug Act of 1983 grants seven years of exclusive marketing rights to a specific drug for a specific orphan indication. The term "orphan drug" refers, generally, to a drug that treats a rare disease affecting fewer than 200,000 persons in the U.S. market exclusivity provisions are distinct from patent protections and apply equally to patented and non-patented drug products.

While the Hatch-Waxman Act addresses the development and approval of generic drugs, the Biologics Price Competition and Innovation Act of 2009 (the "BPCIA"), enacted in the Affordable Care Act (the "ACA") amended the Public Health Service Act (the "PHS Act") to create an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar" to, or "interchangeable", with an FDA-licensed reference product. BPCIA allows for approval of a biosimilar if it is "highly similar" and has no clinically meaningful differences from its approved and existing biological product. Furthermore, as codified in the 2016 Physician Fee Schedule Final Rule, effective January 1, 2016, the physician reimbursement amount for a biosimilar is based on the average sales price (the "ASP") of all National Drug Codes (the "NDCs") assigned to the biosimilars included within the same billing and payment code. In general, this meant that CMS grouped biosimilar products that were licensed with a common reference product with the same payment limit and HCPCS code. However, effective January 1, 2018 under the 2018 Physician Fee Schedule Final Rule, newly approved biosimilar biological products with a common reference product were no longer grouped into the same billing code. Instead, biosimilars are separately coded and paid for under Medicare Part B.

Japan

Manufacturers and sellers of drugs, quasi-drugs, cosmetics, medical devices and regenerative medical products (collectively the "Designated Products") in Japan are subject to the supervision of the MHLW primarily under the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics of Japan ("Pharmaceutical and Medical Device Act" or the "PMD Act"). Under the PMD Act, the relevant licenses must be obtained from the MHLW in order to conduct the business of manufacturing, marketing or selling Designated Products.

Applications for the approval of new products are made through the PMDA. The clinical trial data and other pertinent data must be attached to the application for approval. If the drugs, medical devices or regenerative medical products under application are of types designated by ministerial ordinance of the MHLW, the attached data mentioned above must be obtained in compliance with the standards established by the Minister, such as the Good Laboratory Practice (the "GLP") and the Good Clinical Practice (the "GCP"). Once an application for approval is submitted, a review team is formed, which consists of specialized officials of the PMDA, including experts on chemistry/manufacturing, non-clinical, clinical, and biostatistics. Team evaluation results are passed to the PMDA's external experts, who then report back to the PMDA. After a further team evaluation, a report is provided to the Minister; the Minister makes a final determination for approval and refers this to the Council on Drugs and Foods Sanitation, which then advises the MHLW on final approvability. Marketing and distribution approvals require a review to determine whether or not the product in the application is suitable as a drug to be manufactured and distributed with which a manufacturing and distribution business license for the type of drug concerned has been obtained, and to confirm that the product has been manufactured in a plant compliant with the GMP.

Once the MHLW has approved the application, the company can make the new drug available for physicians to prescribe. After that, the MHLW lists its NHI price within 60 days (or 90 days at the latest) from the approval, and physicians can obtain reimbursement. For some medications, the MHLW requires additional post marketing studies (Phase IV) to further evaluate safety and/or to gather information concerning the quality, efficacy, and safety of the product under specified conditions, in addition to post marketing surveillance including Early Post-marketing Phase Vigilance ("EPPV") based on the risk management plan ("RMP") for all new medications. The MHLW also requires the drug's sponsor to submit periodic safety update reports. Within three months from the specified re examination period, which is designated at the time of the approval of the application for the new product, the company must submit a re examination application to enable the drug's quality, efficacy, and safety to be reassessed against approved labeling by the PMDA.

The PMD Act also provides for special regulations applicable to drugs, quasi-drugs, cosmetics and medical devices made of biological raw materials. These regulations impose various obligations on manufacturers and other persons in relation to manufacturing facilities, explanation to patients, labeling on products, record-keeping and reporting to the Minister.

Under the PMD Act, the Minister may take various measures to supervise manufacturing and marketing license holders of Designated Products. The Minister has the authority to order manufacturing and marketing license holders to temporarily suspend the marketing, leasing or providing of the Designated Products to prevent risks or increases in risks to the public health. Also, the Minister may revoke a license or approval granted to a manufacturing and marketing license holder or order a temporary business suspension under certain limited circumstances such as violation of laws relating to drugs.

European Union

In the EU, there are three main procedures for an application for authorization to market pharmaceutical products in the EU Member States: the Centralized Procedure, the Mutual Recognition Procedure (the "MRP") and the Decentralized Procedure (the "DCP"). It is also possible to obtain a pure national authorization for products intended for commercialization in a single EU Member State only, or for additional indications for licensed products.

Under the Centralized Procedure, applications are made to the EMA for an authorization which is valid throughout the EU. The Centralized Procedure is mandatory for all biotechnology products and for new chemical entities in cancer, neurodegenerative disorders, diabetes, AIDS, autoimmune diseases or other immune dysfunctions, and optional for other new chemical entities or innovative medicinal products or if in the interest of public health. When a pharmaceutical company has gathered data which it believes sufficiently demonstrates a drug's safety, efficacy, and quality, then the company may submit an application to the EMA. The EMA then receives and validates the application, and the Committee for Medicinal Products for Human Use (the "CHMP") appoints a Rapporteur and Co-Rapporteur to lead review of the dossier. The entire review cycle must be completed within 210 days, although there is a "clock stop" at day 120, which allows the company to respond to questions set forth in the Rapporteur and Co-Rapporteur's Assessment Report. After the company's complete response is submitted to the EMA, the clock restarts on day 121. If there are further aspects of the dossier requiring clarification, the EMA will then request an Oral Explanation on day 180, in which case the sponsor must appear before the CHMP to provide the requested additional information. On day 210, the CHMP will then take a vote to recommend the approval or non-approval of the application. The final decision under this Centralized Procedure is a European Community decision which is binding in its entirety on all EU Member States. This decision occurs on average 60 days after a positive CHMP recommendation. In the case of a negative opinion, a written request for re-examination of the opinion can be made by the applicant within a time limit of 15 days from the date of the opinion. The detailed grounds for re-examination must be submitted to the EMA within 60 days from the date of the opinion. In the EU, biosimilars are approved under a specialized pathway of the centralized procedure. Similar to the pathway in the U.S., applicants seek and obtain regulatory approval for a biosimilar once the data exclusivity period for the original reference product has expired relying in part on the data submitted for the original reference product together with data evidencing that the biosimilar is "highly similar" in terms of quality, safety and efficacy to the original reference product authorized in the European Economic Area.

Under both the MRP and DCP, the assessment is led by a single EU Member State, called the Reference Member State (the "RMS"), which then liaises with other EU Member States, known as the concerned member states (the "CMSs"). In the MRP, the company first obtains a marketing authorization in the RMS, which is then recognized by the CMSs in 90 days. In the DCP, the application is done simultaneously in the RMS and all CMSs. During the DCP, the RMS drafts an assessment report within 120 days. Within an additional 90 days, the CMSs review the application and can issue objections or requests for additional information. On day 90, each CMS must be assured that the product is safe and effective, and that it will cause no risks to the public health. Once an agreement has been reached, each member state grants national marketing authorizations for the product.

After the Marketing Authorizations have been granted, the company must submit periodic safety reports to the EMA, if approval was granted under the Centralized Procedure, or to the National Health Authorities, if approval was granted under the DCP or the MRP. In addition, several pharmacovigilance measures must be implemented and monitored including Adverse Event collection, evaluation and expedited reporting and implementation, as well as update Risk Management Plans. For some medications, post approval studies (Phase IV) may be required to complement available data with additional data to evaluate long term effects (called a Post Approval Safety Study) or to gather additional efficacy data (called a Post Approval Efficacy Study).

European Marketing Authorizations have an initial duration of five years. After this first five-year period, the holder of the marketing authorization must apply for its renewal, which may be granted based on the competent authority's full benefit-risk review of the product. Once renewed, the marketing authorization is generally valid for an unlimited period. Any Marketing Authorization which is not followed within three years of its granting by the actual placing on the market in any EU member state of the corresponding medicinal product ceases to be valid.

Third Party Reimbursement and Pricing

We consider domestic and international competitive conditions, such as the price of competing products, in setting and revising the price of our pharmaceutical products. Government regulation also has a significant effect in determining the price of pharmaceutical products in many of the countries in which we operate due to the fact that government policy in many countries has emphasized and purchasers continue to seek large discounts on pharmaceutical products.

United States

In the U.S. our sales are subject to various voluntary and mandatory rebates, which vary depending on the type of coverage and can have a significant impact on our results. The most significant of these are rebates associated with commercial managed care, Medicaid, Medicare and other government programs. In general, the details of these rebates are not disclosed publicly.

Commercial Managed Care

Payers negotiate rebates to reduce the pricing of products, and use formularies to encourage members to utilize preferred products to manage their costs. Exclusion from a formulary, or a disfavored formulary position, can directly reduce product usage. Consolidation of payers, pharmacy benefit managers and specialty pharmacies has resulted, and may continue to result, in increasing rebates and other discounts due to the purchasing power of the consolidated entities. Copay assistance to help patients afford their prescribed drugs may also affect product usage. In recent years, some states such as California and Massachusetts, have passed legislation that limits the use of manufacturer sponsored copay assistance programs, and some payers have limited manufacturer copay assistance benefits to patients.

Medicaid

Medicaid is a state administered program adhering to federal requirements that provides healthcare coverage to eligible low-income adults, children, pregnant women, elderly adults and people with disabilities.

Takeda must pay rebates on purchases of our products under the Medicaid Drug Rebate Program. This includes a mandatory minimum rebate, additional rebates if commercial discounts are greater than the mandatory minimum rebate and an inflation penalty if our prices have increased above inflation. These rebates guarantee that any patient in the Medicaid program can have access to Takeda's products, although there could be significant utilization management imposed by the state. In addition to the mandatory rebates, Takeda may also choose to offer supplemental rebates to a state or Medicaid managed care organization to ensure Takeda's drugs are on the preferred drug list (which is similar to a formulary for Medicaid programs). Takeda must also calculate and report to government agencies the amount of the rebate. The required calculations are complex, and a misrepresentation in the reported information may expose Takeda to penalties. We are required to report any revisions to prior calculations, which could affect the rebate liability for prior quarters.

Medicare

Medicare is a federally run program that provides healthcare to persons aged 65 and over, and certain persons under the age of 65 who have a long-term disability and meet certain eligibility requirements. Drugs are primarily covered under two different benefits for Medicare beneficiaries, Medicare Part B and Medicare Part D. Medicare Part B covers outpatient health and medical services, which includes some drugs under the medical benefit. These drugs tend to be the most biologically complex and are generally administered in a doctor's office or hospital outpatient setting. Medicare Part D is a voluntary drug offering available to Medicare beneficiaries through private health insurance plans that contract with the government to deliver this benefit.

Part B covers drugs that are administered by infusion or injection in a doctor's office or hospital outpatient setting, as well as certain drugs furnished by suppliers. Medicare pays physicians and outpatient hospitals for most separately payable Part B-covered drugs they furnish to beneficiaries at a rate of 106 percent of the manufacturer-reported ASP before sequestration. A product's ASP reflects the average price realized by the manufacturer for sales to all purchasers net of rebates, discounts, and price concessions with certain exceptions. There are no rebates for drugs reimbursed under Part B. Takeda must also calculate and report specific prices to government agencies, including the ASP used by the Medicare Part B program. The required calculations are complex, and a misrepresentation in the reported pricing may expose Takeda to penalties.

Part D covers most of the other outpatient prescription drugs. Except as set forth below with respect to drugs covered by the negotiation provisions of the Inflation Reduction Act ("IRA"), rather than Medicare setting prices administratively, Medicare pays Part D plan sponsors (health plans offering the benefit) that, through their pharmacy benefit managers, contract with pharmacies over payment rates for each prescription filled by an enrollee and negotiate with drug manufacturers for prices and post-sale rebates. Takeda may offer a rebate as part of the negotiation between plan sponsors and manufacturers to ensure that our products are on the formulary. In addition, the Part D program also has an additional mandatory rebate during part of the year, when beneficiaries are in the Medicare Part D coverage gap. Pharmaceutical manufacturers are required to provide a discount of 70% on brand drugs used during that portion of the benefit throughout 2024. In 2022, Congress passed the IRA, which imposes penalties on manufacturers that raise Part D and Part B drug prices, AMP and ASP respectively, faster than the rate of inflation starting in 2022; shifts greater liability to the manufacturer in the Part D program resulting in a 10% discount on brand drugs in the initial coverage phase and 20% in the catastrophic phase, as well as implementing a 2,000 USD out-of-pocket cap for patients on drug expenses starting in 2025; and mandates the negotiation of a new Medicare "maximum fair price" for certain drugs in the Medicare Part D program and the Part B program effective in 2026 and 2028 respectively.

340B and Federal Agency Discounted Pricing

Takeda must offer discounted pricing for purchases by certain designated health care entities and federal agencies under certain federal programs, including the Public Health Service (the "PHS") pharmaceutical pricing program ("340B") and the Federal Supply Schedule (the "FSS").

The 340B program was designed to assist safety net hospitals that serve a disproportionate share of indigent patients by requiring manufacturers, as a stipulation of participation in the Medicaid Drug Rebate Program, to provide deep discounts on covered outpatient drugs. The discounts adhere to a statutory formula, per product, that requires manufacturers to charge no more than a certain price. Entities that may apply to participate in the 340B program include qualifying hospitals, federal grantees, the Centers for Disease Control and Prevention, and the Indian Health Service.

The FSS is a list of contracts and prices for frequently used supplies and services available for purchase by federal agencies and other entities such as the U.S. territories and tribal governments. Although there are no statutory ceilings on prices, the government often uses a favored price as a starting point in negotiations to obtain below-market prices.

Health Care System Reform

For the past few years, there has been an increased focus and downward pressure on pricing which we expect to continue for a variety of circumstantial reasons. There are a number of legislative and regulatory proposals under consideration that would impact how drugs are reimbursed in the U.S., could restrict patient access, and have financial implications for manufacturers.

Japan

In Japan, manufacturers of pharmaceutical products must have new products listed on the National Health Insurance (the "NHI"), a price list published by the MHLW. The NHI price list provides rates for calculating the price of pharmaceutical products used in medical services provided under various public medical care insurance systems. Prices on the NHI price list have been previously subject to revisions based on the actual prices and amounts by which the pharmaceutical products are purchased by medical institutions in Japan, and the average price of previously listed products generally decreases as a result of these price revisions. The Japanese government is currently undertaking healthcare reform initiatives with the goal of sustaining the universal coverage of the NHI program. As part of these initiatives, the annual NHI price list revision was introduced in April 2021, which could lead to more frequent downward price revisions. The government is also addressing the efficient use of drugs, including the further promotion of generic use that slightly fell short of a target of 80% penetration by volume by September 2020 with respect to products for which market exclusivity has expired. In addition, products on the NHI price list nominated based on pre-defined criteria, such as innovativeness and the financial impact, are subject to a cost-effectiveness evaluation under MHLW rules, and subject to price adjustments depending on the outcome of this evaluation.

European Union

In the EU, our operations are subject to significant price and marketing regulations. Many governments in the EU are introducing healthcare reforms to curb increasing healthcare costs. The governments in the EU influence the price of pharmaceutical products through their control of national healthcare systems that fund a large part of the cost of such products to patients. The general downward pressure on healthcare costs, particularly regarding prescription drugs, has been increasing. In addition, prices for marketed products are referenced within and amongst the EU Member States, which further affects pricing in each EU Member State. As an additional control for healthcare budgets, some EU Member States have passed legislation to impose further mandatory rebates for pharmaceutical products and financial claw-backs on the pharmaceutical industry. In this regard, many countries have health technology assessment organizations that use formal economic metrics such as cost-effectiveness to determine prices, coverage and reimbursement of new therapies, and these organizations are expanding in established and emerging markets. We expect that countries will continue to take aggressive actions to seek to reduce expenditures on drugs and biologics. Similarly, fiscal constraints may also affect the extent to which countries are willing to approve new and innovative therapies and/or allow access to new treatments.

The EU is currently undergoing an analysis of the rewards extended for intellectual property of pharmaceutical products as well as the overall regulatory framework for the approval and commercialization of all medicinal products. This may lead to significant changes in the way drugs are approved and commercialized as well as the duration of exclusivity, in particular for orphan drugs. These changes are likely to affect the market within a 3-5-year timeframe.

Furthermore, certain European countries also utilize tendering to secure prescription drugs at controlled price level. Takeda often participates in tendering in these regions, which usually results in a significant price discount.

Other

Many other countries around the world are also taking steps to control prescription drug prices. For example, in 2017, China organized national price negotiations for certain products directly linked to national drug reimbursement, which will apply nationwide both in public and military hospitals. Drug prices in China may further decline due to a stated national policy of reducing healthcare costs, including continued strategic initiatives specifically designed to reduce drug prices. Canada has proposed amendments to its Patented Medicines Regulations that could reduce prices for specialty medicines, such as biologics and medicines for rare diseases. Furthermore, certain other countries also utilize a tendering process to control prescription drugs, in which Takeda often participates.

C. Organizational Structure

We are a holding company and administer our business through a number of subsidiaries worldwide. Information about Takeda's organizational structure, including a list of our subsidiaries, their country of incorporation and residence and our proportion of ownership interest, is included in Note 29 to our audited consolidated financial statements included in this annual report.

D. Property, Plant and Equipment

Our registered head office is located in Osaka, Japan and our global head office is located in Tokyo, Japan. We generally own our facilities or have entered into long-term lease arrangements for them.

As of March 31, 2023, the net book values of the buildings and structures, machinery and vehicles, tools, furniture and fixtures and land we owned were 980.6 billion JPY, 364.8 billion JPY, 43.7 billion JPY and 98.0 billion JPY, respectively. We own the majority of our facilities, none of which are subject to any material encumbrances. We believe our facilities are generally suitable for future needs. Please refer to Item 3.D Risk Factors for more information about risks related to our manufacturing.

The following table describes our major facilities, including production facilities for biopharmaceutical products, plasma-derived therapies and vaccines, as of March 31, 2023:

Group company	Location[1]	Use of facility	Land Area (in square meter)
Takeda Pharmaceutical Company Limited	Chuo-ku,Tokyo, Japan and others	Global Headquarters (Administrative and sales)	16,052
Takeda Pharmaceutical Company Limited	Chuo-ku, Osaka, Japan and others	Head Office (Administrative and sales)	362,305
Takeda Pharmaceutical Company Limited	Yodogawa- ku, Osaka, Japan	Production, research and development	163,694
Takeda Pharmaceutical Company Limited	Hikari-shi, Yamaguchi, Japan	Production, research and development	1,011,061
Takeda Pharmaceutical Company Limited	Narita-shi, Chiba, Japan	Production, research and development	27,644
Takeda Pharmaceutical Company Limited	Fujisawa-shi, Kanagawa, Japan	Research and development	21,009
Baxalta US Inc.	Covington, GA, U.S.	Production and others	508,537

Takeda Pharmaceuticals U.S.A., Inc.	Lexington, MA, U.S.	Administrative, sales and others	—
Shire Human Genetic Therapies, Inc	Lexington, MA, U.S.	Production and others	395,024
BioLife Plasma Services LP	Bannockburn, IL, U.S.	Production and others	428,161
Takeda Development Center Americas, Inc.	Lexington, MA, U.S.	Research, development and others	24,746
Takeda Manufacturing Austria AG	Vienna, Austria	Production and others	368,551
Baxalta Belgium Manufacturing S.A.	Lessines, Belgium	Production and others	150,581
Baxalta Manufacturing S.à r.l.	Neuchatel, Switzerland	Production and others	87,040
Takeda Ireland Limited	Kilruddery, Ireland	Production and others	202,679
Takeda Manufacturing Singapore Pte. Ltd.	Singapore	Production and others	—
Takeda Manufacturing Italia S.p.A.	Rome, Italy	Production and others	109,000
Takeda GmbH	Konstanz, Germany	Production and others	—

Notes:

(1) For subsidiaries, location specified is the main location of the subsidiary. Certain production facilities may be in other locations in the country specified.

(2) Global Headquarters and Head Office mainly consist of buildings, accompanying facilities and lands (includes dormitory and company housing, etc.).

In March 2023, we announced that we will invest in a new manufacturing facility for plasma-derived therapies in Yodogawa-ku, Osaka, Japan. We expect our total investment with funds on hand to amount to 95.0 billion JPY. We expect this construction to start in the fiscal year ended March 31, 2024 and to be completed in the fiscal year ended March 31, 2028.

In January 2023, we started construction of One Cambridge Campus for research and development (R&D) and office space in Cambridge, Massachusetts, the U.S. We expect this construction to be completed in March 2027 and our total investment with funds on hand to amount to 233.3 billion JPY. As of March 31, 2023, the total amount paid on this construction was 0.1 billion JPY. This total investment includes a lease term payment obligation expected to start in 2025 based on a lease agreement we have entered into.

In February 2022, we started construction of a production facility and warehouse in Lessines, Belgium for the manufacturing of plasma-derived therapies. We expect this construction to be completed in December 2024 and our total investment with funds on hand in this construction to amount to 42.1 billion JPY. As of March 31, 2023, the total amount paid on this construction was 7.6 billion JPY.

In November 2016, we started construction of a plant in Singen, Germany, which will be dedicated to the manufacturing for our dengue vaccine candidate (TAK-003). We expect this construction to be completed in March 2024 and our total investment in this construction to amount to 29.9 billion JPY. As of March 31, 2023, the total amount paid on this construction was 29.1 billion JPY.

Environmental Matters

We are subject to laws and regulations concerning the environment, safety matters, regulation of chemicals and product safety in the countries where we manufacture and sell our products or otherwise operate our business. These requirements include regulation of the handling, manufacture, transportation, use and disposal of materials, including the discharge of pollutants into the environment. In the normal course of our business, we are exposed to risks relating to possible releases of hazardous substances into the environment, which could cause environmental or property damage or personal injuries, and which could require remediation of contaminated soil and groundwater, in some cases over many years, regardless of whether the contamination was caused by us, or by previous occupants of the property. See "Item 3. Key Information—D. Risk Factors —*We may incur claims relating to our use, manufacture, handling, storage or disposal of hazardous materials.*"

Item 4A. Unresolved Staff Comments

Not applicable.

Item 5. Operating and Financial Review and Prospects

You should read the following discussion of our operating and financial review and prospects together with our consolidated financial statements included in Item 18 in this annual report. Our consolidated financial statements are prepared in accordance with IFRS, as issued by the International Accounting Standards Board ("IASB"). IFRS includes IAS and related interpretations of the committees (SIC and IFRIC).

The following discussion and analysis contain forward-looking statements that involve risks, uncertainties and assumptions. Our actual results may differ materially from those anticipated in these forward-looking statements as a result of factors, including, but not limited to, those under Item 3. D "Risk Factors" and elsewhere in this annual report.

A. Operating Results

Overview

Takeda is a patient-focused, values-based, research and development ("R&D") driven global biopharmaceutical company, headquartered in Japan. We have grown both organically and through acquisitions, completing a series of major transactions that have resulted in growth in our areas of therapeutic, geographic and pipeline focus. For more information on the history and development of our company, please refer to "Item 4.A. History and Development of the Company".

Our business is organized as a single operating segment, reflecting the presentation of information to our management for the purposes of allocating resources, measuring performance and forecasting future periods. For the fiscal year ended March 31, 2023, our revenue and operating profit were 4,027.5 billion JPY and 490.5 billion JPY, respectively.

Operating Environment

Over the past several years, we have extended our global reach, strengthened our presence in Oncology, GI and Neuroscience, and established a leading position in Rare Diseases and PDT, while adding significant assets to our growing R&D pipeline. Commercially, we have significantly strengthened our presence in the United States, Europe, and Growth and Emerging Markets. We have also accelerated our focus on data and technology to make our business operations more effective and efficient, leading to greater innovation and better serving our stakeholders.

Factors Affecting Our Results of Operations

Our results are affected by global industry trends and our operating environment as described in "Item 3.D. Risk Factors" and "Item 4. Information on the Company" of this annual report and other factors described below.

Patent Protection and Generic Competition

For pharmaceutical products, in particular, patent protection and/or regulatory exclusivity benefit our results of operations by restricting competition. Newly introduced products, particularly those which treat conditions for which alternative treatments may not be readily available, may significantly contribute to sales. However, even protected products must compete with products of other manufacturers based on efficacy, lack of adverse reactions and price. On the other hand, the loss or expiration of patent protection or regulatory exclusivity with respect to any of our principal products could have a material adverse effect on our results of operations, as generic products, which tend to be quickly adopted once introduced, may enter the market. Some of our principal products face, or are expected to face, considerable competition due to the expiration of patent or other intellectual property protection. For example, following the expiration of patent protection over bortezomib, the active ingredient in *VELCADE*, one of our largest selling products in the U.S., a competing bortezomib-containing product has been introduced. This led to a decrease in sales of *VELCADE* in 2022, and further entry of competing products could result in substantial additional declines. Patent protections covering *VYVANSE* are scheduled to expire in the U.S. in August 2023 and a generic version of *AZILVA* was approved by the PMDA in Japan in February 2023 (with a drug price listing for the generic competitor approved in June 2023), which we anticipate will lead to declines in sales for both products in the relevant jurisdictions. In certain cases, generic competitors may successfully challenge the validity of patents, or the manufacturer may decide that the benefits of prematurely launching the generic drug "at risk" outweigh the costs of defending infringement litigation. In situations where the validity of patents or the value of the protection is challenged, we may record impairment losses with respect to the relevant intangible property.

Acquisitions

We may acquire new businesses or assets to expand our R&D capabilities (including expanding into new methodologies) and to acquire new products (whether in the development pipeline or at the marketing stage) or enter other strategic regions. Similarly, we divest from businesses and product lines to maintain our focus on our key growth drivers and to manage our portfolio.

In February 2023, we acquired all of the capital stock of Nimbus Lakshmi, Inc. ("Lakshmi"), a wholly owned subsidiary of Nimbus Therapeutics, LLC ("Nimbus"), that owns or controls the intellectual property rights and other associated assets related to TAK-279, a highly selective oral TYK2 inhibitor. Under the terms of the agreement, we paid Nimbus 4.0 billion USD upfront following the closing of the transaction[(1)], and will pay two milestone payments of 1.0 billion USD each upon achieving annual net sales of 4.0 billion USD and 5.0 billion USD of products developed from the TAK-279 program, formally known as NDI-034858 at Nimbus. In addition, in connection with the transaction, we have agreed to

assume Nimbus's obligations under a January 2022 settlement agreement with Bristol-Myers Squib and its Celgene Corporation subsidiary (collectively, "BMS") to make certain payments to BMS following the achievement of development, regulatory, and sales-based milestones for products developed from the TAK-279 program.

We account for these acquisitions as business combinations or asset acquisitions. For business combinations, we record the assets acquired and liabilities assumed at fair value, which impacts our results in future periods due to costs related to unwinding fair value step-ups of inventory and amortization expense of acquired property, plant and equipment and intangible assets. For assets acquisitions, we record the assets acquired at transaction price. Our results are also impacted due to additional interest expense when an acquisition is financed with incremental borrowings.

As a result of our acquisitions, and the impacts described above, our results year over year may not be comparable.

Note:

(1) Of the 4.0 billion USD upfront payment, 3.0 billion USD was paid in February 2023 and 0.9 billion USD was paid in April 2023. Remaining 0.1 billion USD is scheduled to be paid in August 2023.

Divestitures

In addition to acquisitions, we divested from businesses and product lines to maintain our focus on our key growth drivers and provide additional cash flow to accelerate the repayment of debts. The following are major divestitures completed or announced in the fiscal years ended March 31, 2021, 2022, 2023 and through the issuance of this annual report.

- In November 2020, we completed the sale of a portfolio of select non-core over-the-counter and prescription pharmaceutical products sold exclusively in Asia Pacific to Celltrion Inc., for a total value of 278 million USD, or 26.8 billion JPY, inclusive of milestone payments and a gain of 15.8 billion JPY was recognized in the fiscal year ended March 31, 2021.
- In December 2020, we completed the sale of a portfolio of select non-core prescription pharmaceutical products sold predominantly in Europe and Canada to Cheplapharm for a total value of 562 million USD or 59.4 billion JPY and a gain of 21.4 billion JPY was recognized in the fiscal year ended March 31, 2021.
- In January 2021, we completed the sale of a portfolio of select products sold in Latin America to Hypera S.A. for a total value of 825 million USD or 82.5 billion JPY and a gain of 35.3 billion JPY was recognized in the fiscal year ended March 31, 2021.
- In January 2021, we completed the sale of TachoSil® Fibrin Sealant Patch to Corza Health, Inc. for 350 million EUR or 42.9 billion JPY and a gain of 2.3 billion JPY was recognized in the fiscal year ended March 31, 2021.
- In March 2021, we completed the sale of a portfolio of select products to Orifarm Group for a sales price of 505 million USD or 55.8 billion JPY in cash at closing and approximately 70 million USD or 9.3 billion JPY[(1)] in non-contingent cash to be paid within four years post-closing. In addition, we may receive up to an additional 95 million USD or 12.7 billion JPY[(1)] in potential milestone receipts. Further, a gain of 14.7 billion JPY was recognized in the fiscal year ended March 31, 2021.
- In March 2021, we completed the sale of Takeda Consumer Healthcare Company Limited to Oscar A-Co KK, a company controlled by funds managed by The Blackstone Group Inc. and its affiliates for a total value of 242.0 billion JPY and a gain of 139.5 billion JPY was recognized in the fiscal year ended March 31, 2021.
- In April 2021, we completed the asset transfer associated with a portfolio of select non-core products in Japan to Teijin Pharma Limited for a total value of 133.0 billion JPY. The transaction had a favorable impact of 131.4 billion JPY on profit (loss) before income tax for the fiscal year ended March 31, 2022.
- In March 2022, we completed the sale of a portfolio of non-core prescription pharmaceutical products sold in China to Hasten Biopharmaceutic Co., Ltd. (China) for a total value of 230 million USD or 30.7 billion JPY[(1)] and a gain of 5.6 billion JPY was recognized in the fiscal year ended March 31, 2022.

Note:

(1) Calculated using the Japanese yen—U.S. dollar exchange rate of 133.5 JPY as of March 31, 2023.

Impact of the Availability of Raw Materials

Our results of operations may be negatively impacted if we are not able to internally or externally source critical raw materials. For example, human plasma is a critical raw material in our PDT. Efforts to increase the collection of plasma may require strengthening acquisition and third-party contracting capacities and successful regulatory approval of additional plasma collection facilities and plasma fractionation facilitates.

Foreign Exchange Fluctuations

In the fiscal year ended March 31, 2022 and 2023, 81.5% and 87.3% of our revenue were from outside of Japan. Changes in foreign exchange rates, particularly for the U.S. dollar and the euro, relative to the yen, which is our reporting currency, will impact our revenues and expenses. When the yen weakens against other currencies, our revenues attributable to such other currencies increase, having a positive impact on our results of operations, which may be offset by increased expenses denominated in such currencies. Particularly, our revenues were positively impacted by the weakened yen against other currencies during the fiscal years ended March 31, 2022 and 2023. Conversely, when the yen strengthens against other currencies, our revenues attributable to such currencies decrease, having a negative impact on our results of operations, which may be offset by decreased expenses denominated in such currencies. The following shows revenue at constant exchange rates (CER) for the year ended March 31, 2022 as compared to revenue for the year ended March 31, 2021 and March 31, 2023 as compared to revenue for the year ended March 31, 2022.

	For the fiscal year ended March 31,			
	2021	2022	Change versus the previous year	
	(billions of yen, except percentages)			
Revenue	¥ 3,197.8	¥ 3,569.0	¥ 371.2	11.6 %
Effect of exchange rates		(169.1)		
Revenue at CER	3,197.8	3,399.9	202.1	6.3 %

	For the fiscal year ended March 31,			
	2022	2023	Change versus the previous year	
	(billions of yen, except percentages)			
Revenue	¥ 3,569.0	¥ 4,027.5	¥ 458.5	12.8 %
Effect of exchange rates		(486.6)		
Revenue at CER	3,569.0	3,540.9	(28.1)	(0.8)%

Revenue at CER is not a measure prepared in accordance with IFRS, or a "Non-IFRS Measure." We strongly encourage investors to review our historical financial statements in their entirety and to use measures presented in accordance with IFRS as the primary means of evaluating our performance, value and prospects for the future, and to use this Non-IFRS Measure as a supplemental measure. The most directly comparable measure to revenue at CER that is prepared in accordance with IFRS is revenue, and a reconciliation of revenue at CER to revenue is shown above.

We present revenue at CER because we believe that this measure is useful to investors to better understand the effect of exchange rates on our business, and to understand how our results of operations might have changed from year to year without the effect of fluctuations in exchange rates. These are the primary ways in which our management uses these measures to evaluate our results of operations. We also believe that this is a useful measure for investors as similar performance measures are frequently used by securities analysts, investors and other interested parties in the evaluation of the results of operations of other companies in our industry.

For a given fiscal year, revenue at CER is defined as revenue calculated by translating revenue of the current fiscal year using corresponding exchange rates of the previous fiscal year. The usefulness of this presentation has significant limitations including, but not limited to, that while revenue at CER is calculated using the same exchange rates used to calculate revenue as presented under IFRS for the previous fiscal year, this does not necessarily mean that the transactions entered into during the relevant fiscal year could have been entered into or would have been recorded at the same exchange rates. Moreover, other companies in our industry using similarly titled measures may define and calculate those measures differently than we do, and therefore such measures may not be directly comparable. Accordingly, revenue at constant exchange rates should not be considered in isolation and is not, and should be viewed as, a substitute for revenue as prepared and presented in accordance with IFRS.

To mitigate the risk exposed by foreign exchange fluctuations, we utilize certain hedging measures with respect to some of our significant foreign currency transactions, primarily forward exchange contracts, currency swaps and currency options for individually significant foreign currency transactions.

Periodic Trends

Our revenues were lower in the fourth quarter of each of the fiscal years ended March 31, 2021, 2022, and 2023 partially due to the tendency of wholesalers to increase purchases ahead of the New Year holidays across the region, annual price increases and the reset of annual insurance deductibles in the US at the start of the calendar year.

Critical Accounting Policies

Our consolidated financial statements have been prepared in accordance with IFRS. The preparation of our consolidated financial statements requires management to make estimates and assumptions that affect the reported amount of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reported period. On an ongoing basis, management evaluates its estimates and assumptions. Management bases its estimates and assumptions on historical experience and on various other factors that it believes to be reasonable at the time the estimates and assumptions are made. Actual outcomes may differ from those estimates and assumptions.

We believe the following critical accounting policies are affected by management's estimates and assumptions, changes to which could have a significant impact on our consolidated financial statements.

Revenue Recognition

See Note 3 "Significant Accounting Policies—*Revenue"* to our audited consolidated financial statements

Impairment of Goodwill and Intangible Assets

We review goodwill and intangible assets for impairment whenever events or changes in circumstance indicate that the asset's balance sheet carrying amount may not be recoverable. Goodwill and intangible assets that are currently not amortized are tested for impairment annually and whenever there is any indication of impairment. As of March 31, 2023, we have 4,790.7 billion JPY of goodwill and 4,269.7 billion JPY of intangible assets which in aggregate represent 64.9% of our total assets.

An intangible asset associated with a marketed product is amortized on a straight-line basis over the estimated useful life, which is based on expected patent life, and/or other factors depending on the expected economic benefits of the asset, ranging from 3 to 20 years. Intangible assets related to in-process research and development ("IPR&D") product rights are not amortized until the product is approved for sale by regulatory authorities in specified markets. At that time, we will determine the useful life of the asset and begin amortization.

Goodwill and intangible assets are generally considered impaired when their balance sheet carrying amount exceeds their estimated recoverable amount. The recoverable amount of an intangible asset is estimated for each individual asset or at the larger cash generating unit (CGU) level when cash is generated in combination with other assets. Our cash generating units or group of cash generating units are identified based on the smallest identifiable group of assets that generate independent cash inflows. Goodwill is tested for impairment at the single operating segment level (one CGU), which is the level at which goodwill is monitored for internal management purposes. The estimation of the recoverable value requires us to make a number of assumptions including:

- amount and timing of projected future cash flows;
- behavior of competitors (launch of competing products, marketing initiatives, etc.);
- probability of obtaining regulatory approvals;
- future tax rates;
- terminal growth rate; and
- discount rates.

The significant assumptions used in estimating the amount and timing of future cash flows are the probability of technical and regulatory success related to IPR&D projects and the sales forecast of the products. The sales forecast related to certain products is one of the significant assumptions used in estimating the recoverable amount of goodwill. Events that may result in a change in the assumptions include IPR&D projects that are not successfully developed, fail during development, are abandoned or subject to significant delay or do not receive the relevant regulatory approvals, and/or lower sales projections of certain commercially marketed products typically due to launch of newly competing products, and supply constraints. If these events were to occur, we may not recover the value of the initial or subsequent R&D investments made subsequent to acquisition of the asset project nor realize the future cash flows that we have estimated.

Due to changes in these assumptions in subsequent periods, we have recognized impairment and reversal of impairment related to intangible assets during the periods presented. See Notes 11 and 12 to our audited consolidated financial statements.

Legal Contingencies

We are involved in various legal proceedings primarily related to product liability and commercial liability arising in the normal course of our business. These contingencies are described in detail in Note 32 to our consolidated financial statements.

These and other contingencies are, by their nature, uncertain and based upon complex judgments and probabilities. The factors we consider in developing our provision for litigation and other contingent liability amounts include the merits and jurisdiction of the litigation, the nature and the number of other similar current and past litigation cases, the nature of the product and the current assessment of the science subject to the litigation, and the likelihood of settlement and current state of settlement discussions, if any. In addition, we record a provision for product liability claims incurred, but not filed, to the extent we can formulate a reasonable estimate of their costs based primarily on historical claims experience and data regarding product usage. In cases we may become involved in significant legal proceedings for which it is not possible to make a reliable estimate of the expected financial effect, if any, which may result from ultimate resolution of the proceedings, no provision is recognized for such cases. We also consider the insurance coverage we have to diminish the exposure for periods covered by insurance. In assessing our insurance coverage, we consider the policy coverage limits and exclusions, the potential for denial of coverage by the insurance company, the financial condition of the insurers, and the possibility of and length of time for collection. Any provision and the related estimated insurance recoverable have been reflected on a gross basis as liabilities and assets, respectively, on our consolidated statements of financial position. As of March 31, 2023, we have a provision of 64.3 billion JPY for outstanding legal cases and other disputes.

Income Taxes

We prepare and file our tax returns based on an interpretation of tax laws and regulations, and record estimates based on these judgments and interpretations. In the normal course of business, our tax returns are subject to examination by various tax authorities, which may result in additional tax, interest or penalty assessment by these authorities. Inherent uncertainties exist in estimates of many uncertain tax positions due to changes in tax law resulting from legislation, regulation, and/or as concluded through the various jurisdictions' tax court systems. When we conclude that it is not probable that a tax authority will accept an uncertain tax position, we recognize the best estimate of the expenditure required to settle a tax uncertainty. The amount of unrecognized tax benefits is adjusted for changes in facts and circumstances. For example, adjustments could result from significant amendments to existing tax law, the issuance of regulations or interpretations by the tax authorities, new information obtained during a tax examination, or resolution of a tax examination. We believe our estimates for uncertain tax positions are appropriate and sufficient based on currently known facts and circumstances.

We also assess our deferred tax assets to determine the realizable amount at the end of each period. In assessing the recoverability of deferred tax assets, we consider the scheduled reversal of taxable temporary differences, projected future taxable profits, and tax planning strategies. Future taxable profits according to profitability are estimated based on our business plan. The change in judgment upon determining the revenue forecast related to certain products used for our business plan could have a significant impact on the amount of the deferred tax assets to be recognized. Based on the level of historical taxable profits and projected future taxable profits during the periods in which the temporary differences become deductible, we determine the amount the tax benefits we believe are realizable. As of March 31, 2023, we had unused tax losses, deductible temporary differences, and unused tax credits for which deferred tax assets were not recognized of 1,181.8 billion JPY, 259.8 billion JPY, and 11.2 billion JPY, respectively. A change in our estimates and assumptions in future periods could have a significant impact on our income tax provision.

Restructuring Costs

We incur restructuring costs associated with planned initiatives to reduce our costs or in connection with the integration of our acquisitions. Our most significant restructuring costs are severance payments. We establish a provision for restructuring costs when we have developed a detailed formal plan for the restructuring and a valid expectation has been raised in those affected by the plan that the plan will be implemented. The recognition of restructuring provision requires estimates including timing of payments and the number of individuals impacted by the restructuring. As a result of these estimates, the actual restructuring costs may differ from our estimates.

As of March 31, 2023, we have a provision of 9.0 billion JPY for restructuring costs. See Note 23 to our audited consolidated financial statements for a further description of our restructuring provisions and the change between periods.

Results of Operations

The following table provides selected consolidated statements of profit or loss information for the years ended March 31, 2021, 2022 and 2023.

	For the fiscal year ended March 31,		
	2021	2022	2023
	(billions of yen)		
Revenue	¥ 3,197.8	¥ 3,569.0	¥ 4,027.5
Cost of sales	(994.3)	(1,106.8)	(1,244.1)
Selling, general and administrative expenses	(875.7)	(886.4)	(997.3)
Research and development expenses	(455.8)	(526.1)	(633.3)
Amortization and impairment losses on intangible assets associated with products	(421.9)	(472.9)	(542.4)
Other operating income	318.0	43.1	25.4
Other operating expenses	(258.9)	(159.1)	(145.2)
Operating profit	509.3	460.8	490.5
Finance income	105.5	23.7	62.9
Finance expenses	(248.6)	(166.6)	(169.7)
Share of profit (loss) of investments accounted for using the equity method	0.1	(15.4)	(8.6)
Profit before tax	366.2	302.6	375.1
Income tax (expenses) benefit	9.9	(72.4)	(58.1)
Net profit for the year	¥ 376.2	¥ 230.2	¥ 317.0

Fiscal Year Ended March 31, 2023 compared with the Fiscal Year Ended March 31, 2022

Revenue. Revenue for the fiscal year ended March 31, 2023 was 4,027.5 billion JPY, an increase of 458.5 billion JPY, or 12.8% (CER % change: -0.8%), compared to the previous fiscal year. The increase is primarily attributable to favorable foreign exchange rates and growth from business momentum, fully offsetting the decrease of revenue due to the sale of a portfolio of diabetes products in Japan to Teijin Pharma Limited for 133.0 billion JPY, which was recorded as revenue in the previous fiscal year.

Revenue of our core therapeutic areas (i.e. Gastroenterology ("GI"), Rare Diseases, Plasma-Derived Therapies ("PDT") Immunology, Oncology, and Neuroscience) increased by 628.0 billion JPY, or 21.3%, compared to the previous fiscal year, to 3,572.9 billion JPY. Each of our core therapeutic areas, except Oncology, contributed to positive revenue growth due to favorable foreign exchange rates and growth from business momentum. Generic erosion and intensified competition impacted certain Oncology products in the fiscal year ended March 31, 2023, partially offset by the impacts of favorable foreign exchange rates.

Revenue outside of our core therapeutic areas significantly decreased by 169.6 billion JPY, or 27.2%, compared to the previous fiscal year to 454.6 billion JPY, largely due to the aforementioned non-recurring 133.0 billion JPY selling price of the diabetes portfolio in Japan, which was recorded as revenue in the previous fiscal year.

Revenue by Geographic Region

The following shows revenue by geographic region:

	Billion JPY or percentage				
	For the fiscal year ended March 31,		Change versus the previous fiscal year		
Revenue:	2022	2023		Actual % change	CER % change[1]
Japan[2]	659.0	512.0	(146.9)	(22.3)%	(22.5)%
United States	1,714.4	2,103.8	389.4	22.7 %	2.0 %
Europe and Canada	739.2	842.7	103.5	14.0 %	5.1 %
Asia (excluding Japan)	197.0	225.0	28.0	14.2 %	2.0 %
Latin America	128.5	160.4	31.9	24.8 %	8.0 %
Russia/CIS	62.1	88.4	26.4	42.5 %	9.5 %
Other[3]	68.9	95.2	26.2	38.1 %	41.3 %
Total	3,569.0	4,027.5	458.5	12.8 %	(0.8)%

Notes:
(1) Please refer to "Factors Affecting Our Results of Operations—Foreign Exchange Fluctuations", for the definition.
(2) The 133.0 billion JPY selling price of the sale of diabetes portfolio in Japan is included in the fiscal year ended March 31, 2022.
(3) Other includes the Middle East, Oceania and Africa.

Revenue by Therapeutic Area

The following shows revenue by therapeutic area:

	Billion JPY or percentage				
	For the fiscal year ended March 31,		Change versus the previous fiscal year		
	2022	2023		Actual % change	CER % change[1]
Gastroenterology:					
ENTYVIO	¥ 521.8	¥ 702.7	¥ 181.0	34.7 %	15.2 %
TAKECAB/VOCINTI[2]	102.4	108.7	6.3	6.2	4.1
GATTEX/REVESTIVE	75.8	93.1	17.3	22.9	4.0
DEXILANT	50.8	69.4	18.6	36.7	14.8
PANTOLOC/CONTROLOC[3]	40.3	45.5	5.2	13.0	2.9
ALOFISEL	1.8	2.7	0.9	47.9	35.6
Others	82.9	72.4	(10.5)	(12.7)	(24.0)
Total Gastroenterology	875.7	1,094.5	218.9	25.0	8.7
Rare Diseases:					
Rare Hematology:					
ADVATE	118.5	118.2	(0.3)	(0.3)	(12.4)
ADYNOVATE/ADYNOVI	60.7	66.6	5.8	9.6	(1.0)
FEIBA	39.2	41.3	2.1	5.4	(5.2)
RECOMBINATE	12.3	12.8	0.5	3.8	(13.1)
HEMOFIL/IMMUNATE/IMMUNINE	17.7	19.6	1.9	10.5	0.3
Others	35.3	46.4	11.1	31.4	12.5
Total Rare Hematology	283.7	304.7	21.0	7.4	(5.1)

Billion JPY or percentage

	For the fiscal year ended March 31,		Change versus the previous fiscal year		
	2022	2023		Actual % change	CER % change[1]
Rare Genetics and Other:					
TAKHZYRO	103.2	151.8	48.6	47.0	25.0
ELAPRASE	73.1	85.3	12.2	16.7	5.5
REPLAGAL	51.7	66.7	15.0	29.1	24.2
VPRIV	42.4	48.4	6.0	14.1	2.5
LIVTENCITY	1.3	10.5	9.2	692.4	561.7
Others	55.7	56.0	0.3	0.5	(12.6)
Total Rare Genetics and Other	327.5	418.7	91.2	27.9	13.4
Total Rare Diseases	611.2	723.4	112.2	18.4	4.8
PDT Immunology:					
immunoglobulin	385.9	522.2	136.3	35.3	16.0
albumin	90.0	121.4	31.4	34.9	19.0
Others	31.1	34.8	3.7	12.0	(4.2)
Total PDT Immunology	507.0	678.4	171.5	33.8	15.3
Oncology:					
LEUPLIN/ENANTONE	106.5	111.3	4.9	4.6	(0.3)
NINLARO	91.2	92.7	1.5	1.6	(12.2)
ADCETRIS	69.2	83.9	14.7	21.3	13.5
ICLUSIG	34.9	47.2	12.3	35.4	15.9
VELCADE	110.0	27.8	(82.3)	(74.8)	(78.6)
ALUNBRIG	13.6	20.6	6.9	50.7	35.2
EXKIVITY	1.0	3.7	2.8	288.1	228.4
Others	42.4	51.6	9.2	21.7	20.7
Total Oncology	468.7	438.7	(30.0)	(6.4)	(14.4)
Neuroscience:					
VYVANSE/ELVANSE	327.1	459.3	132.2	40.4	18.2
TRINTELLIX	82.3	100.1	17.8	21.6	2.1
Others	72.9	78.3	5.4	7.4	(4.0)
Total Neuroscience	482.3	637.7	155.4	32.2	12.1
Other:					
AZILVA-F[2]	76.3	72.9	(3.4)	(4.5)	(4.5)
LOTRIGA	32.7	16.7	(16.0)	(48.8)	(48.8)
Others[4]	515.2	365.0	(150.2)	(29.2)	(35.4)
Total Other	624.2	454.6	(169.6)	(27.2)	(32.4)
Total	¥ 3,569.0	¥ 4,027.5	¥ 458.5	12.8 %	(0.8)%

Notes:
(1) Please refer to "Factors Affecting Our Results of Operations—Foreign Exchange Fluctuations", for the definition.
(2) The figures include the amounts of fixed dose combinations and blister packs.
(3) Generic name: pantoprazole
(4) The figure for the year ended March 31, 2022 includes the 133.0 billion JPY selling price on sales of four diabetes products (NESINA, LIOVEL, INISYNC and ZAFATEK) in Japan to Teijin Pharma Limited recorded as revenue. As Takeda transferred only the assets, marketing rights and, eventually, marketing authorization associated with the pharmaceutical products which do not entail transfer of employees or associated contracts, Takeda applied IFRS 15 to the transaction and recorded the selling price in revenue.

Year-on-year change in revenue for this fiscal year in each of our main therapeutic areas was primarily attributable to the following products:

- *GI.* In Gastroenterology, revenue was 1,094.5 billion JPY, a year-on-year increase of 218.9 billion JPY, or 25.0% (CER % change: 8.7%).

  Sales of ENTYVIO (for ulcerative colitis ("UC") and Crohn's disease ("CD")), Takeda's top-selling product, were 702.7 billion JPY in total, an increase of 181.0 billion JPY, or 34.7%, versus the previous fiscal year. Sales in the U.S. were 491.9 billion JPY, an increase of 142.4 billion JPY, or 40.7%, driven by favorable foreign exchange rates and a continued increase in the first line biologic inflammatory bowel disease ("IBD") population both in UC and CD. Sales in Europe and Canada were 162.5 billion JPY, an increase of 26.5 billion JPY, or 19.5%, supported by continued launches of the subcutaneous formulation and favorable foreign exchange rates. Sales in the Growth and Emerging Markets were 34.9 billion JPY, an increase of 9.9 billion JPY, or 39.6%, primarily led by growth in Brazil.

  Sales of DEXILANT (for acid reflux disease) were 69.4 billion JPY, an increase of 18.6 billion JPY, or 36.7%, versus the previous fiscal year, due to the increased sales of authorized generics in the U.S. and favorable foreign exchange rates.

  Sales of GATTEX/REVESTIVE (for short bowel syndrome) were 93.1 billion JPY, an increase of 17.3 billion JPY, or 22.9%, versus the previous fiscal year, primarily due to increased market penetration after launch in Japan, pediatric indication demand, and favorable foreign exchange rates.

  Sales of TAKECAB/VOCINTI (for acid-related diseases) were 108.7 billion JPY, an increase of 6.3 billion JPY, or 6.2%, versus the previous fiscal year, primarily due to increased sales in China, partially offset by the decrease of sales in Japan due to a negative impact from the market expansion re-pricing applied in April 2022, despite an increase in prescription volume.

  Sales of PENTASA (for UC), included in Others, were 8.4 billion JPY, a decrease of 11.8 billion JPY, or 58.3%, versus the previous fiscal year, due to generic erosion in the U.S. from May 2022.

- *Rare Diseases*. In Rare Diseases, revenue was 723.4 billion JPY, a year-on-year increase of 112.2 billion JPY, or 18.4% (CER % change: 4.8%).

  Revenue of Rare Hematology was 304.7 billion JPY, a year-on-year increase of 21.0 billion JPY, or 7.4% (CER % change: -5.1%).

  Sales of ADYNOVATE/ADYNOVI (for hemophilia A) were 66.6 billion JPY, an increase of 5.8 billion JPY, or 9.6%, and sales of FEIBA (for hemophilia A and B) were 41.3 billion JPY, an increase of 2.1 billion JPY, or 5.4%, versus the previous fiscal year, primarily due to favorable foreign exchange rates largely offset by negative impacts from competition in the U.S.

  Sales of other Rare Hematology products in aggregate increased year-on-year, primarily due to additional indications, newly consolidated products, and favorable foreign exchange rates.

  Revenue of Rare Genetics and Other was 418.7 billion JPY, a year-on-year increase of 91.2 billion JPY, or 27.9% (CER % change: 13.4%).

  Sales of TAKHZYRO (for hereditary angioedema) were 151.8 billion JPY, an increase of 48.6 billion JPY, or 47.0%, versus the previous fiscal year, driven by continued strong demand in the U.S., geographic expansion, and favorable foreign exchange rates.

  Sales of REPLAGAL (for Fabry disease) were 66.7 billion JPY, an increase of 15.0 billion JPY, or 29.1%, versus the previous fiscal year, primarily due to the succession to Takeda of manufacturing and marketing rights in Japan upon expiration of the relevant license agreement in February 2022 and strong demand in the Growth and Emerging Markets.

  Sales of other enzyme replacement therapies ELAPRASE (for Hunter syndrome) and VPRIV (for Gaucher disease) were 85.3 billion JPY, an increase of 12.2 billion JPY, or 16.7%, and 48.4 billion JPY, an increase of 6.0 billion JPY, or 14.1%, respectively, primarily due to favorable foreign exchange rates.

  Sales of LIVTENCITY (for post-transplant cytomegalovirus ("CMV") infection/disease), which was first launched in the U.S. in December 2021, followed by several other countries, were 10.5 billion JPY in the current fiscal year.

- *PDT Immunology.* In Plasma-Derived Therapies ("PDT") Immunology, revenue was 678.4 billion JPY, a year-on-year increase of 171.5 billion JPY, or 33.8% (CER % change: 15.3%).

  Sales of immunoglobulin products in aggregate were 522.2 billion JPY, an increase of 136.3 billion JPY, or 35.3%, versus the previous fiscal year. Sales of each of our three global immunoglobulin brands marked double digit percentage of revenue growth, due to continued strong demand globally and growing supply, especially in the U.S., where the pandemic pressure is now easing, as well as favorable foreign exchange rates. Those include GAMMAGARD LIQUID/KIOVIG (for the treatment of primary immunodeficiency ("PID") and multifocal motor neuropathy ("MMN")), and subcutaneous immunoglobulin therapies (CUVITRU and HYQVIA) which are growing due to their benefit to patients and convenience in administration compared to intravenous therapies.

  Sales of albumin products in aggregate, including HUMAN ALBUMIN and FLEXBUMIN (primarily used for hypovolemia and hypoalbuminemia), were 121.4 billion JPY, an increase of 31.4 billion JPY, or 34.9%, versus the previous fiscal year, driven by strong albumin demand in the U.S. and China and favorable exchange rates.

- *Oncology.* In Oncology, revenue was 438.7 billion JPY, a year-on-year decrease of 30.0 billion JPY, or 6.4% (CER % change: -14.4%), impacted by the rapid generic erosion of VELCADE (for multiple myeloma) sales in the U.S.

  Sales of VELCADE were 27.8 billion JPY, a decrease of 82.3 billion JPY, or 74.8%, versus the previous fiscal year, predominantly due to multiple generic entrants in the U.S. starting in May 2022.

Sales of ADCETRIS (for malignant lymphomas) were 83.9 billion JPY, an increase of 14.7 billion JPY, or 21.3%, versus the previous fiscal year, led by strong growth in countries such as Argentina, Italy and Japan.

Sales of ICLUSIG (for leukemia) were 47.2 billion JPY, an increase of 12.3 billion JPY, or 35.4%, versus the previous fiscal year, due to steady growth in the U.S. and favorable foreign exchange rates.

Sales of ALUNBRIG (for non-small cell lung cancer) were 20.6 billion JPY, an increase of 6.9 billion JPY, or 50.7%, versus the previous fiscal year, benefiting from strong demand in European countries, Growth and Emerging Markets such as China, and Japan.

Sales of ZEJULA (for ovarian cancer), included in Others, were 12.9 billion JPY, an increase of 4.9 billion JPY, or 61.7%, versus the previous fiscal year, primarily led by increased sales in Japan due to a newly launched tablet formulation in June 2022 in addition to existing capsule formulation.

Sales of LEUPLIN/ENANTONE (for endometriosis, uterine fibroids, premenopausal breast cancer, prostate cancer, etc.), an off-patent product, were 111.3 billion JPY, an increase of 4.9 billion JPY, or 4.6%, versus the previous fiscal year, mainly due to favorable foreign exchange rates.

Sales of NINLARO (for multiple myeloma) were 92.7 billion JPY, an increase of 1.5 billion JPY, or 1.6%, versus the previous fiscal year, aided by favorable foreign exchange rates, which were offset partially by intensified competition and decreased demand mainly in the U.S.

Sales of EXKIVITY (for non-small cell lung cancer), which was first launched in the U.S. in September 2021, followed by several other countries, were 3.7 billion JPY in the current fiscal year.

- *Neuroscience.* In Neuroscience, revenue was 637.7 billion JPY, a year-on-year increase of 155.4 billion JPY, or 32.2% (CER % change: 12.1%).

  Sales of VYVANSE/ELVANSE (for attention deficit hyperactivity disorder (“ADHD”)) were 459.3 billion JPY, an increase of 132.2 billion JPY, or 40.4%, versus the previous fiscal year, mainly due to the growth of the adult market including an impact from a shortage of generic versions of the instant release formulation of ADDERALL in the U.S. and favorable foreign exchange rates.

  Sales of TRINTELLIX (for major depressive disorder (“MDD”)) were 100.1 billion JPY, an increase of 17.8 billion JPY, or 21.6%, versus the previous fiscal year, due to increasing prescriptions in Japan and favorable foreign exchange rates.

  Sales of ADDERALL XR (for ADHD), included in Others, were 28.6 billion JPY, an increase of 7.7 billion JPY, or 36.9%, versus the previous fiscal year, mainly due to a shortage of generic versions of the instant release formulation marketed by competitors in the U.S. and favorable foreign exchange rates.

Cost of Sales. Cost of Sales increased by 137.2 billion JPY, or 12.4% (CER % change: -0.1%), to 1,244.1 billion JPY. The increase was predominantly due to the depreciation of the yen in the current fiscal year.

Selling, General and Administrative (SG&A) expenses. SG&A expenses increased by 110.9 billion JPY, or 12.5% (CER % change: -0.9%) compared to the previous fiscal year, to 997.3 billion JPY, mainly due to the impact from the depreciation of the yen in the current fiscal year.

Research and Development (R&D) expenses. R&D expenses increased by 107.2 billion JPY, or 20.4% (CER % change: 3.5%) compared to the previous fiscal year, to 633.3 billion JPY, mainly due to the impact from the depreciation of the yen in the current fiscal year.

Amortization and Impairment Losses on Intangible Assets Associated with Products. Amortization and Impairment Losses on Intangible Assets Associated with Products increased by 69.5 billion JPY, or 14.7% (CER % change: -3.2%) compared to the previous fiscal year, to 542.4 billion JPY, mainly due to the impact from the depreciation of the yen in the current fiscal year.

Other Operating Income. Other Operating Income was 25.4 billion JPY, a decrease of 17.7 billion JPY, or 41.0% (CER % change: -44.2%), compared to the previous fiscal year primarily due to a change in fair value of financial assets and liabilities associated with contingent consideration arrangements recognized and certain settlement proceeds recorded in the previous fiscal year.

Other Operating Expenses. Other Operating Expenses were 145.2 billion JPY, a decrease of 13.8 billion JPY, or 8.7% (CER % change: -21.1%), compared to the previous fiscal year, primarily due to decreases in restructuring expenses attributable to the substantially completed Shire integration in the previous fiscal year and valuation reserve for pre-launch inventory, partially offset by increases in other reserves and provisions including those for certain assets related to option fees Takeda paid as part of collaboration agreements and increase due to the impact from the depreciation of the yen in the current fiscal year.

Operating Profit. As a result of the above factors, Operating Profit increased by 29.7 billion JPY, or 6.4% (CER % change: -1.8%) compared to the previous fiscal year to 490.5 billion JPY.

Net Finance Expenses. Net Finance Expenses were 106.8 billion JPY in the current fiscal year, a decrease of 36.1 billion JPY, or 25.3% (CER % change: -28.8%) compared to Net Finance Expenses of 142.9 billion JPY for the previous fiscal year. This decrease was mainly driven by a positive impact from the remeasurement of warrants to purchase stocks of companies held by Takeda.

Share of Loss of Investments Accounted for Using the Equity Method. Share of Loss of Investments Accounted for Using the Equity Method was 8.6 billion JPY, a decrease of 6.7 billion JPY, or 43.8% (CER % change: -50.6%), compared to the previous fiscal year. The decrease is mainly due to the negative impact from Takeda's share of loss on an investment held by Takeda Ventures, Inc. recorded in the previous fiscal year.

Income Tax Expenses. Income Tax Expenses were 58.1 billion JPY, a decrease of 14.4 billion JPY, or 19.8% (CER % change; -18.0%), compared to the previous fiscal year. This decrease was primarily due to a tax charge of 65.4 billion JPY for tax and interest, net of 0.5 billion JPY of associated tax benefit, arising from tax assessment involving Irish taxation of the break fee Shire received from AbbVie in connection with the terminated offer to acquire Shire made by AbbVie in 2014 in the previous fiscal year as well as increased tax benefits from recognition of deferred tax assets. These decreases were partially offset by the benefits from the US state tax rate change in the previous fiscal year, in addition to higher pretax earnings.

Net Profit for the Year. Net Profit for the Year increased by 86.9 billion JPY, or 37.7% (CER % change: 23.3%), compared to the previous fiscal year to 317.0 billion JPY.

Fiscal Year Ended March 31, 2022 compared with the Fiscal Year Ended March 31, 2021

Revenue. Revenue for the fiscal year ended March 31, 2022 was 3,569.0 billion JPY, an increase of 371.2 billion JPY, or 11.6%, compared to the previous fiscal year. Excluding the impact from fluctuations in foreign exchange rates, which was calculated by translating revenue of the fiscal year ended March 31, 2022, using corresponding exchange rates in the previous fiscal year, the increase in revenue was 6.3%. In April 2021, Takeda completed the sale of a portfolio of diabetes products in Japan to Teijin Pharma Limited for 133.0 billion JPY, which was recorded as revenue and accounted for 4.2 percentage points ("pp") of the increase in revenue. Excluding this selling price from revenue for the fiscal year ended March 31, 2022, the increase was 7.4%.

Revenue of our core therapeutic areas in the business (i.e. Gastroenterology ("GI"), Rare Diseases, Plasma-Derived Therapies ("PDT") Immunology, Oncology, and Neuroscience) increased by 321.1 billion JPY, or 12.2%, compared to the previous fiscal year to 2,944.9 billion JPY. Each of our core therapeutic areas contributed to positive revenue growth; however, Rare Diseases would have declined if not for the positive impact of the depreciation of the yen. Intensified competition impacted some products in this area, especially treatments for Rare Hematology. Although the impact of the global spread of COVID-19 did not have a material effect on our overall consolidated revenue for the fiscal year ended March 31, 2022, we have experienced some disruption to certain products in the second half of the fiscal year due to the spread of the Omicron variant, including shipping delays and fewer diagnostic procedures.

Revenue outside of our core therapeutic areas increased by 50.1 billion JPY, or 8.7%, compared to the previous fiscal year to 624.1 billion JPY, due to the 133.0 billion JPY selling price of the diabetes portfolio in Japan and other increases including revenue from distributing Moderna's COVID-19 vaccine, SPIKEVAX Intramuscular Injection, in Japan, offsetting the impact from prior divestitures.

The following shows revenue by geographic region:

	For the fiscal year ended March 31,			
	2021		2022	
	(billions of yen, percentages are the proportion to total revenue)			
Revenue:				
Japan[(1)]	¥ 559.7	17.5%	¥ 659.0	18.5%
United States	1,567.9	49.0	1,714.4	48.0
Europe and Canada	666.2	20.8	739.2	20.7
Asia (excluding Japan)	156.2	4.9	197.0	5.5
Latin America	121.6	3.8	128.5	3.6
Russia/CIS	57.6	1.8	62.1	1.7
Other[(2)]	68.5	2.1	68.9	1.9
Total	¥ 3,197.8	100.0%	¥ 3,569.0	100.0%

Notes:
(1) The 133.0 billion JPY selling price of the sale of diabetes portfolio in Japan is included in the fiscal year ended March 31, 2022.
(2) Other includes the Middle East, Oceania and Africa.

We rely on certain key prescription drug products to generate a significant portion of our revenue. The following table provides revenue for such key products by therapeutic area.

	For the Year Ended March 31,			
	2021	2022	Change versus the previous year	
	(billions of yen, except for percentages)			
Gastroenterology:				
ENTYVIO	¥ 429.3	¥ 521.8	¥ 92.5	21.5 %
TAKECAB-F [1]	84.8	102.4	17.6	20.7
GATTEX/REVESTIVE	64.6	75.8	11.2	17.3
DEXILANT	55.6	50.8	(4.8)	(8.7)
PANTOLOC/CONTROLOC [2]	43.1	40.3	(2.8)	(6.6)
ALOFISEL	0.8	1.8	1.1	135.1
Others	99.7	82.9	(16.8)	(16.8)
Total Gastroenterology	777.8	875.7	97.9	12.6
Rare Diseases:				
Rare Metabolic:				
ELAPRASE	68.8	73.1	4.3	6.3
REPLAGAL	51.8	51.7	(0.0)	(0.1)
VPRIV	38.5	42.4	3.9	10.1
NATPARA/NATPAR	3.6	5.4	1.8	50.7
Total Rare Metabolic	162.6	172.6	10.0	6.1
Rare Hematology:				
ADVATE	128.5	118.5	(10.0)	(7.8)
ADYNOVATE/ADYNOVI	58.1	60.7	2.7	4.6
FEIBA	44.5	39.2	(5.3)	(12.0)
RECOMBINATE	13.4	12.3	(1.1)	(8.2)
Others	45.3	53.0	7.7	17.0
Total Rare Hematology	289.8	283.7	(6.1)	(2.1)
Hereditary Angioedema:				
TAKHZYRO	86.7	103.2	16.5	19.1
FIRAZYR	26.8	26.7	(0.1)	(0.5)
Others	25.8	23.7	(2.1)	(8.3)
Total Hereditary Angioedema	139.3	153.6	14.3	10.2
Others	—	1.3	1.3	—
Total Rare Diseases	591.7	611.2	19.5	3.3
PDT Immunology:				
immunoglobulin	334.9	385.9	51.0	15.2
albumin	57.6	90.0	32.5	56.4
Others	27.9	31.1	3.1	11.2
Total PDT Immunology	420.4	507.0	86.6	20.6

	For the Year Ended March 31,			
	2021	2022	Change versus the previous year	
	(billions of yen, except for percentages)			
Oncology:				
VELCADE	101.1	110.0	8.9	8.8
LEUPLIN/ENANTONE	95.4	106.5	11.1	11.6
NINLARO	87.4	91.2	3.8	4.4
ADCETRIS	59.4	69.2	9.8	16.4
ICLUSIG	34.2	34.9	0.7	1.9
ALUNBRIG	8.8	13.6	4.8	54.9
Others	30.2	43.3	13.1	43.4
Total Oncology	416.5	468.7	52.2	12.5
Neuroscience:				
VYVANSE/ELVANSE	271.5	327.1	55.5	20.4
TRINTELLIX	68.9	82.3	13.4	19.5
Others	76.9	72.9	(4.0)	(5.2)
Total Neuroscience	417.3	482.3	65.0	15.6
Other:				
AZILVA-F [(1)]	82.2	76.3	(5.9)	(7.2)
LOTRIGA	31.8	32.7	0.9	2.9
Others [(3)]	460.1	515.2	55.1	12.0
Total Other	574.1	624.2	50.1	8.7
Total	¥ 3,197.8	¥ 3,569.0	¥ 371.2	11.6 %

Notes:
(1) The figures include the amounts of fixed dose combinations and blister packs.
(2) Generic name: pantoprazole
(3) The figure for the years ended March 31, 2021 includes the revenue of Takeda Consumer Healthcare Company Limited, which was divested on March 31, 2021. The figure for the year ended March 31, 2022 includes the 133.0 billion JPY selling price on sales of four diabetes products (NESINA, LIOVEL, INISYNC and ZAFATEK) in Japan to Teijin Pharma Limited, which was divested on April 1, 2021.

Year-on-year change in revenue for this fiscal year in each of our main therapeutic areas was primarily attributable to the following products:

- *GI.* In Gastroenterology, revenue was 875.7 billion JPY, a year-on-year increase of 97.9 billion JPY, or 12.6%. Growth was driven by Takeda's top-selling product ENTYVIO (for ulcerative colitis ("UC") and Crohn's disease ("CD")), with sales of 521.8 billion JPY, a year-on-year increase of 92.5 billion JPY, or 21.5%. Sales in the U.S. increased by 55.2 billion JPY, or 18.8%, to 349.5 billion JPY driven by increases in the first line biologic inflammatory bowel disease ("IBD") population both in UC and CD. Sales in Europe and Canada increased by 27.0 billion JPY, or 24.8%, to 136.0 billion JPY. In Growth and Emerging Markets, sales increased by 7.8 billion JPY, or 45.7%, to 25.0 billion JPY, primarily driven by increased sales in Brazil and China. Sales of TAKECAB (for acid-related diseases) were 102.4 billion JPY, an increase of 17.6 billion JPY, or 20.7%, versus the previous fiscal year. This increase was mainly driven by the expansion of new prescriptions in the Japanese market due to TAKECAB's efficacy in reflux esophagitis and the prevention of recurrence of gastric and duodenal ulcers during low-dose aspirin administration. Sales of GATTEX/REVESTIVE (for short bowel syndrome) were 75.8 billion JPY, an increase of 11.2 billion JPY, or 17.3%, primarily due to increased market penetration and new country launches including Japan. Sales of AMITIZA (for chronic constipation), included in Others, decreased by 14.8 billion JPY, or 69.6%, to 6.5 billion JPY, due to generic entrants in the U.S. in January 2021.

- *Rare Diseases*. In Rare Diseases, revenue was 611.2 billion JPY, a year-on-year increase of 19.5 billion JPY, or 3.3%.

  Revenue in Rare Metabolic increased by 10.0 billion JPY, or 6.1%, compared to the previous fiscal year to 172.6 billion JPY. Sales of enzyme replacement therapies ELAPRASE (for Hunter syndrome) and VPRIV (for Gaucher diseases) increased primarily in Europe and Growth and Emerging Markets, and in the U.S., Europe and Growth and Emerging Markets, respectively.

  Revenue in Rare Hematology decreased by 6.1 billion JPY, or 2.1%, to 283.7 billion JPY. Sales of ADVATE decreased by 10.0 billion JPY, or 7.8%, to 118.5 billion JPY. Sales of ADYNOVATE/ADYNOVI increased by 2.7 billion JPY, or 4.6%, to 60.7 billion JPY. Both products were impacted by the competitive landscape in the hemophilia A non-inhibitors market in the U.S. FEIBA sales decreased by 5.3 billion JPY, or 12.0%, to 39.2 billion JPY, negatively impacted by the difference in timing of government tenders in Growth and Emerging Markets.

Revenue in Hereditary Angioedema ("HAE") was 153.6 billion JPY, a year-on-year increase of 14.3 billion JPY, or 10.2%. Sales of TAKHZYRO were 103.2 billion JPY, an increase of 16.5 billion JPY, or 19.1%, versus the previous fiscal year primarily due to expansion of the prophylactic market, continued geographic expansion and strong patient uptake. Sales of CINRYZE, included in Others, decreased by 2.6 billion JPY, or 11.8%, to 19.3 billion JPY, primarily due to conversion to TAKHZYRO and a shift to newer agents marketed by competitors.

- *PDT Immunology.* In Plasma-Derived Therapies ("PDT") Immunology, revenue increased by 86.6 billion JPY, or 20.6%, compared to the previous fiscal year to 507.0 billion JPY. Aggregate sales of immunoglobulin products were 385.9 billion JPY, an increase of 51.0 billion JPY, or 15.2%, compared to the previous fiscal year. In particular, sales of GAMMAGARD LIQUID/KIOVIG (for the treatment of primary immunodeficiency ("PID") and multifocal motor neuropathy ("MMN")) increased due to continued strong demand globally and enabled by growing supply. In addition, CUVITRU and HYQVIA, which are SCIG (subcutaneous immunoglobulin) therapies, marked double digit percentage of revenue growth. Aggregate sales of albumin products including HUMAN ALBUMIN and FLEXBUMIN (primarily used for hypovolemia and hypoalbuminemia) were 90.0 billion JPY, an increase of 32.5 billion JPY, or 56.4%, versus the previous fiscal year driven by higher sales following the resolution of the supply interruption which impacted HUMAN ALBUMIN for release in China in the second half of the previous fiscal year, in addition to strong FLEXBUMIN demand in China and the U.S.

- *Oncology.* In Oncology, revenue was 468.7 billion JPY, a year-on-year increase of 52.2 billion JPY, or 12.5%. Sales of VELCADE (for multiple myeloma) increased by 8.9 billion JPY, or 8.8% versus the previous fiscal year to 110.0 billion JPY. This growth was driven by an increase in U.S. sales of 10.4 billion JPY, or 10.8%, versus the previous fiscal year. This reflects a rebound in demand after lower sales in the first quarter of the previous fiscal year, when prescribers favored orally administered products over infusions or injections early in the COVID-19 pandemic. In addition, increased use of VELCADE as part of initial treatment for new patients contributed to the growth this year in the U.S. Royalty income outside the U.S. decreased due to continued generic erosion. Sales of LEUPLIN/ENANTONE (generic name: leuprorelin) (for endometriosis, uterine fibroids, premenopausal breast cancer, prostatic cancer, etc.), an off-patented product, increased by 11.1 billion JPY, or 11.6%, versus the previous fiscal year to 106.5 billion JPY mainly driven by an increased supply in the U.S. which was partially offset by a decrease in Japan due to generic erosion and competition. Sales of NINLARO (for multiple myeloma) were 91.2 billion JPY, an increase of 3.8 billion JPY, or 4.4%, versus the previous fiscal year. In the U.S., NINLARO growth was adversely impacted by a temporary demand increase favoring oral options early in the previous fiscal year due to COVID-19, and by demand slow-downs in the fourth quarter of the current fiscal year. There has been continued strong growth in other regions, particularly in China and Japan. Sales of ADCETRIS (for malignant lymphomas) increased by 9.8 billion JPY, or 16.4% versus the previous fiscal year to 69.2 billion JPY, led by strong growth in sales in Growth and Emerging Markets, particularly in China where it was approved in May 2020. Sales of ALUNBRIG (for non-small cell lung cancer) were 13.6 billion JPY, an increase of 4.8 billion JPY, or 54.9% due to new launches and market penetration around the world.

- *Neuroscience.* In Neuroscience, revenue was 482.3 billion JPY, a year-on-year increase of 65.0 billion JPY, or 15.6%. Sales of VYVANSE/ELVANSE (for attention deficit hyperactivity disorder ("ADHD")) were 327.1 billion JPY, an increase of 55.5 billion JPY, or 20.4%, versus the previous fiscal year. VYVANSE/ELVANSE has been negatively affected by COVID-19 during the course of the pandemic, most notably during periods when stay-at-home restrictions have been in place reducing patient visits, subsequent diagnoses and creating temporary discontinuation of medication. While the trend has been fluctuating since 2020, overall, there has been a positive impact from increasing prescriptions in the current fiscal year. Sales of TRINTELLIX (for major depressive disorder ("MDD")) were 82.3 billion JPY, an increase of 13.4 billion JPY, or 19.5%, versus the previous fiscal year, due to increasing prescriptions in the U.S. and in Japan. The increase of these products was partially offset by the decrease of other neuroscience products such as REMINYL (for Alzheimer's disease), included in Others, attributable to the continued impact of competition from generic products in Japan.

Cost of Sales. Cost of Sales increased by 112.5 billion JPY, or 11.3%, to 1,106.8 billion JPY. The increase was primarily due to the depreciation of the yen and a sales increase of products with higher cost of sales ratio for the fiscal year ended March 31, 2022. The increase was partially offset by a 46.5 billion JPY decrease in non-cash charges related to the unwind of the fair value step up on acquired inventory recognized in connection with the acquisition of Shire as well as a decrease of cost of sales from divested products of the previous fiscal year.

Selling, General and Administrative (SG&A) expenses. SG&A expenses increased by 10.7 billion JPY, or 1.2%, to 886.4 billion JPY for the fiscal year ended March 31, 2022, mainly due to the impact from the depreciation of the yen in the current fiscal year.

Research and Development (R&D) expenses. R&D expenses increased by 70.3 billion JPY, or 15.4%, to 526.1 billion JPY for the fiscal year ended March 31, 2022, mainly due to further investment in prioritized new molecular entities as well as the impact from the depreciation of the yen in the current fiscal year.

Amortization and Impairment Losses on Intangible Assets Associated with Products. Amortization and Impairment Losses on Intangible Assets Associated with Products increased by 51.1 billion JPY, or 12.1%, to 472.9 billion JPY for the fiscal year ended March 31, 2022 mainly due to impairment charges of certain in-process R&D assets including TAK-721 due to discontinuation of the program and intangible assets related to NATPARA resulting from the reassessment of the recoverable amount and recorded in the current fiscal year.

Other Operating Income. Other Operating Income was 43.1 billion JPY, a decrease of 274.9 billion JPY, or 86.4%, for the fiscal year ended March 31, 2022, predominantly driven by the effect of a 228.9 billion JPY divestiture gain in the previous fiscal year. This included a 139.5 billion JPY gain on sale of shares and relevant assets of Takeda Consumer Healthcare Company Ltd., and other non-core assets amounting to 89.4 billion JPY. The decrease is also due to a 60.2 billion JPY revaluation gain recorded in the previous fiscal year, triggered by an update to previously recognized liabilities for pipeline compound SHP647 and certain associated rights ("SHP647"), to reflect management's decision to terminate the clinical trial program following the European Commission's decision in May 2020 to release Takeda's obligation to divest SHP647.

Other Operating Expenses. Other Operating Expenses were 159.1 billion JPY, a decrease of 99.8 billion JPY, or 38.6%, for the fiscal year ended March 31, 2022. This is mainly attributable to a 72.9 billion JPY loss recognized in the previous year from changes in the fair value of financial assets associated with contingent consideration arrangements from the divestment of XIIDRA and a 32.0 billion JPY decrease in restructuring expenses mainly attributable to the decrease in Shire integration costs.

Operating Profit. As a result of the above factors, Operating Profit decreased by 48.4 billion JPY, or 9.5%, for the fiscal year ended March 31, 2022 to 460.8 billion JPY.

Net Finance Expenses. Net Finance Expenses were 142.9 billion JPY for the fiscal year ended March 31, 2022, a decrease of 0.2 billion JPY, or 0.1%, compared to the previous fiscal year. These results include a negative impact from the remeasurement of a warrant to purchase stocks of a company held by Takeda that was offset by factors including a gain on prior equity method investments related to the acquisition of Maverick Therapeutics, Inc. in April 2021 recorded in the current fiscal year and a decrease in net interest expense primarily driven by the reduction in outstanding balances of bonds and loans.

Share of Loss of Investments Accounted for Using the Equity Method. Share of Loss of Investments Accounted for Using the Equity Method was 15.4 billion JPY, a decrease of 15.4 billion JPY compared to Share of Profit of Investments Accounted for Using the Equity Method of 0.1 billion JPY for the previous fiscal year, mainly due to the negative impact from Takeda's share of loss on an investment held by Takeda Ventures, Inc. This negative impact was partially offset by a decrease of Takeda's share of impairment loss recognized by Teva Takeda Pharma Ltd.

Income Tax Expenses. Income Tax Expenses were 72.4 billion JPY for the fiscal year ended March 31, 2022, compared to income tax benefit of 9.9 billion JPY for the previous fiscal year. This was primarily due to a decrease of tax benefits from internal entity restructuring transactions and a current fiscal year's tax charge of 65.4 billion JPY for tax and interest, net of 0.5 billion JPY of associated tax benefit, arising from tax assessment involving Irish taxation of the break fee Shire received from AbbVie in connection with the terminated offer to acquire Shire made by AbbVie in 2014. There was also a decrease in tax benefits from the recognition of previously unrecognized deferred tax assets. These unfavorable changes were partially offset by a tax charge on divestitures in the previous fiscal year, decreased deferred tax liabilities for unremitted earnings in foreign subsidiaries, and lower pretax earnings.

Net Profit for the Year. Net Profit for the Year decreased by 146.0 billion JPY, or 38.8%, for the fiscal year ended March 31, 2022 to 230.2 billion JPY.

B. Liquidity and Capital Resources

Sources and Uses of Liquidity

Our liquidity requirements mainly relate to operating cash, capital expenditures, contractual obligations, repayment of indebtedness and payment of interest and dividends. Our operating cash requirements include cash outlays for R&D expenses, milestone payments, sales and marketing expenses, personnel and other general and administrative costs and raw material costs. Income tax payments also require significant cash outlays as well as working capital financing.

Our capital expenditures for tangible assets consist primarily of enhancing and streamlining our production facilities, replacing fully depreciated items, and promoting efficiency of our operations. Our capital expenditures for intangible assets represent mainly milestone payments related to licensed products, where such assets have been acquired from third-party partners, as well as software development expenditures. Our capital expenditures, which consist of additions to property, plant and equipment and intangible assets recorded on our consolidated statements of financial position, were 330.7 billion JPY and 239.9 billion JPY and 898.7 billion JPY for the fiscal years ended March 31, 2021, 2022 and 2023, respectively. As of March 31, 2023, we had contractual commitments for the acquisition of property, plant and equipment of 15.3 billion JPY. In addition, we had certain contractual agreements related to the acquisition of intangible assets as of March 31, 2023. See Note 32 to our consolidated financial statements for a description of our milestone payments of intangible assets. As part of our capital management, we periodically assess our level of capital expenditures in light of capital needs, market and other conditions and other relevant factors.

Our dividend payments for the fiscal years ended March 31, 2021, 2022 and 2023 were 283.7 billion JPY, 284.2 billion JPY and 280.8 billion JPY, respectively. Takeda has historically returned capital to shareholders using dividends at an annual level of 180 JPY per share, consisting of interim and fiscal year-end dividends of 90 JPY per share. It is our intention to return capital to shareholders using dividends at an annual level of 188 JPY per share in the fiscal year ending March 31, 2024, consisting of interim and fiscal year-end dividends of 94 JPY per share. See “Item 8. Financial Information—A. Consolidated Statements and Other Financial Information-Dividends” for a description of our dividend policy.

We are required to make interest and principal payments on our outstanding borrowings. As of March 31, 2023, we had 104.2 billion JPY of interest due within one year and 340.4 billion JPY of principal payments on our borrowings due within one year. See “*Borrowings and Financial Obligations.*”

Our primary sources of liquidity include cash and cash equivalents on hand, short-term commercial paper, committed borrowing lines from financial institutions and long-term debt financing that includes bonds from the global capital markets. Additionally, we have access to short-term uncommitted borrowing lines of 150.0 billion JPY and 750 million USD from financial institutions as of March 31, 2022 and 2023, respectively.

We monitor and adjust the amount of foreign cash based on projected cash flow requirements. As the majority of our business is conducted outside Japan, we hold a significant portion of cash outside of Japan. Our ability to use foreign cash to fund cash flow requirements in Japan may be impacted by local regulations and, to a lesser extent, income taxes associated with transferring cash to Japan.

We continue to closely monitor our funding situation and do not currently anticipate experiencing funding or liquidity shortfalls in the short term as a result of general market conditions. In addition to the ability to seek additional funding (if needed) from market and other sources, we may also manage our funding and liquidity needs by reconsidering, to the extent necessary and appropriate, our capital expenditure plans.

As of March 31, 2023, we held 533.5 billion JPY in cash and cash equivalents on hand, of which 125.8 billion JPY was cash temporarily held on behalf of third parties related to vaccine operations and a trade receivables sales program. In addition, Takeda had access to 700.0 billion JPY in an undrawn bank commitment line. We believe that working capital is sufficient for our current business requirements. Furthermore, we continually seek to ensure that our level of liquidity and access to capital market funding continues to be maintained to successfully support our business operations.

Consolidated Cash Flows

The following table shows information about our consolidated cash flows during the fiscal years ended March 31, 2021, 2022 and 2023:

	For the fiscal year ended March 31,		
	2021	2022	2023
	(billions of yen)		
Net cash from operating activities	¥ 1,010.9	¥ 1,123.1	¥ 977.2
Net cash from (used in) investing activities	393.5	(198.1)	(607.1)
Net cash used in financing activities	(1,088.4)	(1,070.3)	(709.1)
Net increase (decrease) in cash and cash equivalents	¥ 316.1	¥ (145.3)	¥ (339.1)
Cash and cash equivalents at the beginning of the year	637.6	966.2	849.7
Effects of exchange rate changes on cash and cash equivalents	12.5	28.8	22.9
Cash and cash equivalents at the end of the year	¥ 966.2	¥ 849.7	¥ 533.5

Fiscal Year Ended March 31, 2023 compared with the Fiscal Year Ended March 31, 2022

Net cash from operating activities was 977.2 billion JPY for the fiscal year ended March 31, 2023 compared to 1,123.1 billion JPY for the fiscal year ended March 31, 2022. The decrease of 145.9 billion JPY was primarily driven by an unfavorable impact from net of changes in assets and liabilities related to the operating activities, mainly due to a change in trade and other payables and increased income taxes paid. These were partially offset by higher net profit for the year adjusted for non-cash items and other adjustments.

Net cash used in investing activities was 607.1 billion JPY for the fiscal year ended March 31, 2023 compared to 198.1 billion JPY for the fiscal year ended March 31, 2022. The increase of 409.0 billion JPY was mainly due to an increase of 430.2 billion JPY in acquisition of intangible assets primarily resulting from the acquisition of Nimbus Lakshmi Inc.* for the current year, partially offset by a decrease of 49.7 billion JPY in acquisition of business (net of cash and cash equivalents acquired).

* Of the 4.0 billion USD upfront payment, 3.0 billion USD was paid in February 2023 and 0.9 billion USD was paid in April 2023. Remaining 0.1 billion USD is scheduled to be paid in August 2023.

Net cash used in financing activities was 709.1 billion JPY for the fiscal year ended March 31, 2023 compared to 1,070.3 billion JPY for the fiscal year ended March 31, 2022. The decrease of 361.1 billion JPY was mainly due to a decrease in repayments of bonds and long-term loans, net of proceeds from issuance of bonds and long-term loans upon refinancing, of 279.1 billion JPY, as well as an increase in commercial paper drawings of 40.0 billion JPY. In addition, there was a decrease in purchase of treasury shares of 50.6 billion JPY resulting from the higher share buybacks conducted in the previous year compared to the current year.

Fiscal Year Ended March 31, 2022 compared with the Fiscal Year Ended March 31, 2021

Net cash from operating activities was 1,123.1 billion JPY for the fiscal year ended March 31, 2022 compared to 1,010.9 billion JPY for the fiscal year ended March 31, 2021. The increase of 112.2 billion JPY was primarily driven by higher net profit for the period adjusted for non-cash items and other adjustments, including gain on divestment of business and subsidiaries as well as the income relating to the release from the obligation to divest the pipeline compound SHP647 and certain associated rights in the previous fiscal year. In addition, there was a decrease in trade and other receivables mainly due to the trade receivables sales program put in place in the current fiscal year. These favorable impacts were partially offset by a decrease of other financial liabilities primarily attributable to a decrease of deposits restricted to certain vaccine operations and a decrease in provisions due to payments.

Net cash used in investing activities was 198.1 billion JPY for the fiscal year ended March 31, 2022 compared to net cash from investing activities of 393.5 billion JPY for the fiscal year ended March 31, 2021. This increase in net cash used of 591.7 billion JPY was mainly due to a decrease of 502.2 billion JPY in proceeds from sales of business (net of cash and cash equivalents divested) reflecting the sales of the non-core assets in the previous fiscal year, a decrease of 57.7 billion JPY in proceeds from sales and redemptions of investments, an increase of 49.7 billion JPY in the acquisition of businesses (net of cash and cash equivalents acquired), and a decrease of 44.6 billion JPY in proceeds from sales of property, plant and equipment. These were partially offset by a decrease of 62.5 billion JPY in acquisition of intangible assets.

Net cash used in financing activities was 1,070.3 billion JPY for the fiscal year ended March 31, 2022 compared to 1,088.4 billion JPY for the fiscal year ended March 31, 2021. The decrease of 18.1 billion JPY was mainly due to a net increase in short-term loans and commercial papers of 149.0 billion JPY and a decrease in payments for settlement of forward rate agreements related to bonds of 34.8 billion JPY, partially offset by an increase in repayments of bonds and long-term loans, net of proceeds from issuance of bonds upon refinancing, of 88.6 billion JPY and an increase in purchase of treasury shares of 75.4 billion JPY mainly due to the share buybacks conducted in the current fiscal year.

Borrowings and Financial Obligations

Our total bonds and loans were 4,345.4 billion JPY and 4,382.3 billion JPY as of March 31, 2022 and 2023, respectively. These borrowings include unsecured bonds and senior notes issued by Takeda, bilateral and syndicated loans entered into by the Company, borrowings incurred to fund a portion of the Shire Acquisition, debt assumed in connection with the Shire Acquisition and debt refinanced and are included in our consolidated statements of financial position. Our borrowings are mainly incurred in connection with acquisitions and therefore are not exposed to seasonality.

On April 23, 2022, Takeda redeemed 219 million USD of unsecured U.S. dollar-denominated senior notes issued in June 2015 in advance of their original maturity date of June 23, 2022. Following this, on October 27, 2022, Takeda redeemed 1,000 million USD of unsecured U.S. dollar-denominated senior notes issued in November 2018 in advance of their original maturity date of November 26, 2023. Furthermore, on November 21, 2022, Takeda redeemed 750 million EUR of unsecured floating rate senior notes issued in November 2018 on their maturity date. On March 31, 2023, Takeda repaid 75 billion JPY in bilateral loans falling due and on the same day entered into new bilateral loans of 75 billion JPY maturing on March 30, 2029. Takeda also had short term commercial paper drawings outstanding of 40 billion JPY as of March 31, 2023, noting that there were no commercial paper drawings as of March 31, 2022.

As of March 31, 2023, we had certain outstanding borrowings that contained financial covenants. A key financial covenant requires Takeda's ratio of consolidated net debt to adjusted EBITDA, as defined in the loan agreements, for the previous twelve-month period to not surpass certain levels as of March 31 and September 30 of each year. Takeda was in compliance with all financial covenants as of March 31, 2023 in a similar manner to the prior year ended March 31, 2022. There are no restrictions on the ability to draw from the 700 billion JPY commitment line that was put in place in 2019 and matures at the end of September 2026.

We currently have a Japanese unsecured commercial paper program in place to facilitate short-term liquidity management. The total amount drawn on the commercial paper program was nil as of March 31, 2022 and 40 billion JPY as of March 31, 2023. We further have access to short-term uncommitted lines of 150 billion JPY and 750 million USD which were undrawn as of March 31, 2022 and 2023, respectively.

For further description of our borrowings, see Note 20 to our audited consolidated financial statements.

Credit Ratings

Our credit ratings, which reflect each rating agency's opinion of our financial strength, operating performance and ability to meet our obligations, as of the date of this annual report are as follows:

Rating Agency	Category	Rating	Outlook	Rating Structure
S&P Global Ratings	Issuer credit rating/foreign currency long-term and local currency long-term	BBB+	Stable	Fourth highest of 11 rating categories and first within the category based on modifiers (e.g. BBB+, BBB and BBB- are within the same category).
	Issuer credit rating (short-term)	A-2		Second highest of six rating categories
Moody's	Long-term issuer rating and Long-term senior unsecured rating	Baa1*	Stable*	Fourth highest of nine rating categories and first within the category based on modifiers (e.g. Baa1, Baa2 and Baa3 are within the same category).

* Moody's revised the long-term issuer credit rating from Baa2 to Baa1 and changed the outlook from Positive to Stable on June 26, 2023.

The ratings are not a recommendation to buy, sell or hold securities. The ratings are subject to revision or withdrawal at any time by the assigning rating agency. Each of the financial strength ratings should be evaluated independently.

Material Cash Requirements from Contractual and Other Obligations

Material Contractual Obligations

The following table summarizes our contractual obligations as of March 31, 2023:

	Total contractual amount[1]	Within one year	Between one and three years	Between three and five years	More than five years
			(billions of yen)		
Bonds and loans: [2] [3]					
Bonds [4]	¥ 4,640.2	¥ 331.2	¥ 768.4	¥ 849.9	¥ 2,690.7
Loans	767.6	113.4	153.5	425.2	75.5
Purchase obligations for property, plant and equipment	15.3	15.3	—	—	—
Repayment of lease liabilities	666.0	59.6	107.2	87.4	411.7
Contributions to defined benefit plans [5]	12.5	12.5	—	—	—
Total [6] [7]	¥ 6,101.6	¥ 532.0	¥ 1,029.1	¥ 1,362.5	¥ 3,177.9

Notes:

(1) Obligations denominated in currencies other than Japanese yen have been translated into Japanese yen using the exchange rates as of March 31, 2023 and may fluctuate due to changes in exchange rates.
(2) Repayment obligations may be accelerated if we breach the relevant covenants under the relevant instruments.
(3) Includes interest payment obligations.
(4) The contractual amount of bonds in "Between one and three years" includes a 500.0 billion JPY principal amount of hybrid subordinated bonds ("Hybrid Bonds") as Takeda may make an early repayment of all of the principal of the Hybrid Bonds on each interest payment date beginning October 6, 2024. For details of the principal and interest rate associated with the Hybrid Bond, see Note 20 to our audited consolidated financial statements.
(5) Pension and post-retirement contributions cannot be determined beyond the fiscal year ending March 31, 2024 because the timing of funding is uncertain and dependent on future movements in interest rates and investment returns, changes in laws and regulations and other variables.
(6) Does not include contractual obligations whose timing we are unable to estimate, including defined benefit obligations, litigation reserves and long-term income tax liabilities and does not include liabilities recorded at fair value as amounts will fluctuate based on any changes in fair value including derivative liabilities and financial liabilities associated with contingent consideration arrangements. The carrying amounts of derivative liabilities and financial liabilities associated with contingent consideration arrangements as of March 31, 2023 were 40.7 billion JPY and 8.1 billion JPY, respectively. Milestone payments that are dependent on the occurrence of certain future events are not included.
(7) Does not include purchase orders entered into for purchases made in the normal course of business.

Milestone Payments

Under the terms of our collaborations with third parties for the development of new products, we may be required to make payments for the achievement of certain milestones related to the development of pipeline products and the launch and subsequent marketing of new products. As of March 31, 2023, the contractual amount of potential milestone payments totaled 1,455.6 billion JPY, in each case excluding potential commercial milestone payments. See Note 13 and 32 to our audited consolidated financial statements for further details.

C. Research and Development, Patents and Licenses, etc.

The information required by this item is set forth in "Item 4. Information on the Company—B. Business Overview—Research and Development" of this annual report.

D. Trend Information

The information required by this item is set forth in "Item 5.A. Operating Results—Factors Affecting Our Results of Operations—Periodic Trends" of this annual report.

E. Critical Accounting Estimates

The requirements of this item are not applicable to Takeda, as it prepares its financial statements in accordance with IFRS. Takeda presents information about its critical accounting policies under "Item 5.A. Operating Results—Critical Accounting Policies" of this annual report.

Item 6. Directors, Senior Management and Employees

A. Directors and Senior Management

Directors

The following table provides information about Directors of the Company as of the date of this annual report.

Name (Date of birth)	Responsibilities and status within Takeda	Business experience	End of term
Christophe Weber (November 14, 1966)	Representative Director, President and Chief Executive Officer ("CEO")	Christophe Weber is President and CEO of Takeda. He joined Takeda in April 2014 as Chief Operating Officer and Corporate Officer, was named President and Representative Director in June 2014 and was subsequently appointed Chief Executive Officer in April 2015. Since September 2020, Mr. Weber has also served as Head of Global Business of Takeda Pharmaceuticals U.S.A., Inc. Prior to joining Takeda, Mr. Weber held positions of increasing responsibility at GlaxoSmithKline, including President and General Manager at GlaxoSmithKline Vaccines, Chief Executive Officer of GlaxoSmithKline Biologicals SA in Belgium, and member of the GlaxoSmithKline global Corporate Executive Team. From 2008 to 2010, Mr. Weber served as Asia Pacific SVP and Regional Director at GlaxoSmithKline Asia Pacific in Singapore.	Note 1
Costa Saroukos (April 15, 1971)	Director and Chief Financial Officer ("CFO")	Costa Saroukos has been Takeda's Chief Financial Officer since April 2018. He was appointed as Corporate Officer in April 2018 and Director in June 2019. Mr. Saroukos has over 20 years of experience in both the private and public sectors, having held a number of finance leadership positions with financial responsibility for businesses in over 100 countries across Asia-Pacific, Europe, Africa and the Middle East. Mr. Saroukos has been with Takeda since May 2015, as CFO of the Europe and Canada business unit, significantly contributing to the transformation of the business unit towards a specialty healthcare provider. Prior to joining Takeda, Mr. Saroukos was at Allergan as Head of Finance and Business Development for the Asia-Pacific region, including China and Japan. He was also Finance Director for Greater China and Japan. Previously, he spent 13 years at Merck & Co. in roles of increasing responsibility, including Executive Finance Director for EEMEA (Eastern Europe, Middle East and Africa), Finance Director of South Korea and Head of Internal Audit Asia Pacific and Global Joint Ventures.	Note 1
Andrew S. Plump, M.D., Ph.D. (October 13, 1965)	Director and President, Research and Development	Andrew S. Plump, MD., Ph.D., is the President of Research and Development at Takeda. Dr. Plump joined Takeda as Chief Medical and Scientific Officer ("CMSO") in 2015. In his position, he leads our global research and development organization, where he provides strategic direction and oversight. Prior to joining Takeda, Dr. Plump served as Senior Vice President, Research and Translational Medicine, Deputy to the President of research and development at Sanofi, where he was responsible for global research and translational medicine across all therapeutic areas. Dr. Plump also spent more than 10 years at Merck in a Clinical Pharmacology group, working on programs in neurodegeneration, immunology, metabolism and infectious diseases.	Note 1

Name (Date of birth)	Responsibilities and status within Takeda	Business experience	End of term
Masami Iijima (September 23, 1950)	External Director and Chair of the Board of Directors	Masami Iijima served as External Director who is a member of the Audit and Supervisory Committee of Takeda from June 2021 to June 2022, and was appointed External Director of Takeda and Chair of the Board of Directors meeting in June 2022. Mr. Iijima currently also serves as Counselor of Mitsui & Co., Ltd., External Director of SoftBank Group Corp., Counsellor at Bank of Japan and External Director of Kajima Corporation . Mr. Iijima started his career at Mitsui & Co., Ltd. in April 1974. At Mitsui & Co., Ltd., he served in several senior leadership positions including Chairman of the Board of Directors and Representative Director, President and Chief Executive Officer.	Note 1
Olivier Bohuon (January 3, 1959)	External Director	Olivier Bohuon has been an External Director with Takeda since January 2019. Prior to his appointment, Mr. Bohuon was an External Director of Shire. Mr. Bohuon currently also holds the position of External Director and Chairman at Majorelle International, External Director at Virbac SA, External Director at AlgoTherapeutix SAS and External Director at Reckitt Benckiser Group plc. Mr. Bohuon has previously served as External Director and Chairman at LEO Pharma A/S, Chief Executive Officer of Smith & Nephew plc, Chief Executive Officer and President of Pierre Fabre Group SA and as President of Abbott Pharmaceuticals; a division of US-based Abbott Laboratories. He has also held diverse commercial leadership positions at GlaxoSmithKline and its predecessor companies in France.	Note 1
Jean-Luc Butel (November 8, 1956)	External Director	Jean-Luc Butel served as External Director and member of the Audit and Supervisory Committee of Takeda from June 2016 to June 2019. He was appointed External Director who is not a member of the Audit and Supervisory Committee of Takeda in June 2019. He currently also serves as Global Healthcare Advisor, President of K8 Global Pte. Ltd., External Director of Novo Holdings A/S and External Director of Rani Therapeutics. Mr. Butel previously served as President, International, Corporate Vice President and Operating Committee Member of Baxter International Inc. and has held leadership positions at Medtronic, Inc., Johnson & Johnson, Becton, Dickinson and Company and Nippon Becton Dickinson Company, Ltd.	Note 1
Ian Clark (August 27, 1960)	External Director	Ian Clark has been an External Director with Takeda since January 2019. Prior to his appointment, Mr. Clark was an External Director of Shire plc. He also currently holds External Directorships at Corvus Pharmaceuticals, Inc., Guardant Health, Inc., AVROBIO Inc, and Olema Pharmaceuticals, Inc. Mr. Clark served as CEO and Director of Genentech Inc. (part of the Roche Group) and Head of North American Commercial Operations for Roche until 2016. From 2003 to 2010 he held the positions of Head of Global Product Strategy and Chief Marketing Officer, Executive Vice President—Commercial Operations and Senior Vice President and General Manager—BioOncology at Genentech.	Note 1
Steven Gillis, PhD (April 25, 1953)	External Director	Steven Gillis has been an External Director with Takeda since January 2019. Prior to his appointment, he was an External Director of Shire plc. He also currently holds the positions of Managing Director at ARCH Venture Partners, External Director and Chairman of Codiak BioSciences, Inc., External Director of Homology Medicines, Inc. and External Director and Chairman, VBI Vaccines, Inc. He was a founder and Director of Corixa Corporation, acquired by GlaxoSmithKline in 2005, and before that a founder and Director of Immunex Corporation.	Note 1

Name (Date of birth)	Responsibilities and status within Takeda	Business experience	End of term
John Maraganore, PhD (October 11, 1962)	External Director	John Maraganore was appointed External Director of Takeda in June 2022. He currently also serves as Scientific Advisory Board member of Alnylam Pharmaceuticals, Inc., and holds External Directorships at Agios Pharmaceuticals, Inc., Beam Therapeutics, Inc., Kymera Therapeutics, Inc. and ProKidney Corporation. He previously served as Senior Vice President and Strategic Product Development at Millennium Pharmaceuticals, Inc., Director and CEO of Alnylam Pharmaceuticals, Inc. and Chairperson of Biotechnology Innovation Organization.	Note 1
Michel Orsinger (September 15, 1957)	External Director	Michel Orsinger has served as External Director who is not a member of the Audit and Supervisory Committee of Takeda from June 2016 to June 2019, and as External Director who is a member of the Audit and Supervisory Committee of Takeda from June 2019 to June 2022. He was appointed External Director who is not a member of the Audit and Supervisory Committee of Takeda in June 2022. He previously served as a Member of Global Management Team of Johnson & Johnson, Worldwide Chairman, Global Orthopedics Group of DePuy Synthes Companies of Johnson & Johnson and President and Chief Executive Officer and Chief Operating Officer of Synthes, Inc. (currently Johnson & Johnson). He has also held several leadership positions at Novartis AG, including Chief Executive Officer and President of OTC Division Worldwide, Consumer Health; President of Global Medical Nutrition, Consumer Health; and Regional President of Europe, Middle East and Africa, Consumer Health.	Note 1
Miki Tsusaka (April 24, 1963)	External Director	Miki Tsusaka was appointed External Director of Takeda in June 2023. She currently also serves as President of Microsoft Japan Co., Ltd. Prior to joining Microsoft Japan, she was a Senior Partner and Managing Director at Boston Consulting Group (BCG). She established strategic consulting groups specializing in marketing, sales and pricing strategy development and led the expansion of BCG's service areas. As for BCG's operation, she was a member of the Executive Committee for two three-year terms and served as Chief Marketing Officer (CMO) as well.	Note 1
Koji Hatsukawa (September 25, 1951)	External Director (Head of Audit and Supervisory Committee)	Koji Hatsukawa has served as External Director and member of the Audit and Supervisory Committee of Takeda since June 2016. He was appointed Head of Audit and Supervisory Committee in June 2019. He currently also serves as External Audit and Supervisory Board Member of Fujitsu Limited. Mr. Hatsukawa started his career at Price Waterhouse accounting office in March 1974. Mr. Hatsukawa has previously served CEO of PricewaterhouseCoopers Arata and has held leadership positions at ChuoAoyama PricewaterhouseCoopers and Aoyama Audit Corporation. In addition, he has also served as External Audit and Supervisory Board Member of Accordia Golf co., Ltd. as well as Audit and Supervisory Board Member of The Norinchukin Bank.	Note 2

Name (Date of birth)	Responsibilities and status within Takeda	Business experience	End of term
Yoshiaki Fujimori (July 3, 1951)	External Director (Audit and Supervisory Committee Member)	Yoshiaki Fujimori served as External Director who is not a member of the Audit and Supervisory Committee of Takeda from June 2016 to June 2022 and was appointed External Director who is a member of the Audit and Supervisory Committee of Takeda in June 2022. Mr. Fujimori currently also serves as Senior Executive Advisor of CVC Asia Pacific (Japan) Kabushiki Kaisha, External Director and Chairman of Oracle Corporation Japan, External Director of Riraku K.K. and Trygroup Inc. He previously served as External Director of Tokyo Electric Power Company, Incorporated (currently Tokyo Electric Power Company Holdings, Incorporated), External Director of Toshiba Corporation, External Director of Shiseido Company, Limited and in a number of senior leadership positions within the LIXIL Group, including Representative Director, Chairman and CEO of LIXIL Corporation. Mr. Fujimori has also served in a number of senior positions in the General Electric Group, including Chairman of GE Japan Corporation and Chairman, President and CEO of General Electric Japan Ltd.	Note 2
Emiko Higashi (November 6, 1958)	External Director (Audit and Supervisory Committee Member)	Emiko Higashi served as External Director who is not a member of the Audit and Supervisory Committee of Takeda from June 2016 to June 2019. She was appointed External Director who is a member of the Audit and Supervisory Committee of Takeda in June 2019. She currently also serves as Managing Director of Tomon Partners, LLC, External Director of KLA Corporation, External Director of Rambus Inc, and External Director of Rapidus Corporation. Ms. Higashi previously served as External Director of MetLife Insurance K.K., External Director of InvenSense Inc., External Director of Sanken Electric Co., Ltd., External Director of One Equity Partners Open Water I Corporation, CEO of Gilo Ventures, LLC, Managing Director of Investment Banking, Merrill Lynch & Co. and Director of Wasserstein Perella & Co., Inc.	Note 2
Kimberly A. Reed (March 11, 1971)	External Director (Audit and Supervisory Committee Member)	Kimberly A. Reed was appointed External Director who is a member of the Audit and Supervisory Committee of Takeda in June 2022. She currently also serves as Distinguished Fellow of Council on Competitiveness, External Director of Momentus, Inc. and External Director of Hannon Armstrong Sustainable Infrastructure Capital, Inc. Ms. Reed previously served as Counsel for United States House of Representatives, Senior Advisor to United States Secretaries of the Treasury, Director and Chief Executive Officer of Community Development Financial Institutions Fund, Vice President, Financial Markets Policy Relations of Lehman Brothers, President of International Food Information Council Foundation, and Chairman of the Board of Directors, President, and Chief Executive Officer of Export-Import Bank of the United States.	Note 2

Notes:

(1) The term of office for Directors who are not members of the Audit and Supervisory Committee is from the end of the ordinary general meeting of shareholders for the fiscal year ended March 31, 2023 through the end of the ordinary general meeting of shareholders for the fiscal year ending March 31, 2024.

(2) The term of office for Directors who are also Audit and Supervisory Committee members is two years. The term of office for these Directors who are also Audit and Supervisory Committee members is from the end of the ordinary general meeting of shareholders for the fiscal year ended March 31, 2022 through the end of the ordinary general meeting of shareholders for the fiscal year ending March 31, 2024.

Takeda Executive Team

The following table presents biographical information about the members of the Takeda Executive Team as of the date of this annual report. For more information about the Takeda Executive Team, see "—C. Board Practices—Takeda Executive Team."

Name (Date of birth)	Responsibilities and status within Takeda	Business experience
Marcello Agosti (June 2, 1971)	Global Business Development Officer	Marcello Agosti is Global Business Development Officer for Takeda Pharmaceutical Company Limited. and is responsible for Takeda's business development activities, including M&A and Corporate Development. Mr. Agosti led the Shire acquisition and several other strategic acquisitions for Takeda, including ARIAD Pharmaceuticals, TiGenix and Nimbus. He also spearheaded a number of strategic divestments of non-core assets as part of Takeda's commitment after the Shire acquisition. Marcello and his group continue to be active on inbound transactions in Takeda's core therapy areas. Prior to joining Takeda, Mr. Agosti worked in business development at Novartis in the U.K. and Switzerland. Before joining the pharmaceutical industry, he was a consultant at McKinsey & Company. He holds an MBA from the University of Oxford and a Business Administration degree from Bocconi University, Milan.
Teresa Bitetti (September 21, 1962)	President, Global Oncology Business Unit	Teresa Bitetti is President of Global Oncology Business Unit of Takeda Pharmaceutical Company Limited. She joined the company in April 2019 and is responsible for oncology business activities around the world, overseeing a global portfolio consisting of therapies in hematological malignancies and lung solid tumor. Prior to joining Takeda, Ms. Bitetti spent more than 20 years at Bristol-Myers Squibb (BMS), where she held several leadership roles, including Senior Vice President, Head of Worldwide Oncology Commercialization. During her tenure, she oversaw the launch of Opdivo in the U.S. market and significantly enhanced the long-term strategic direction of the immuno-oncology portfolio. Before BMS, Ms. Bitetti held various roles of increasing responsibility at Mobil Oil Corporation, where she was part of the Capital Markets Group and responsible for the investment of Mobil's worldwide pension assets. Ms. Bitetti holds an MBA in Finance from the Darden School of Business at the University of Virginia and a B.A. in Classical Civilization from Wellesley College.
Lauren Duprey (May 13, 1984)	Chief Human Resources Officer	Lauren Duprey is Chief Human Resources Officer of Takeda Pharmaceutical Company Limited with responsibility for delivering an exceptional people experience across the globe. She joined Takeda in August 2019 as Head of Human Resources (HR) for U.S. Business Unit, Global Product & Launch Strategy and the U.S. People Advisory Group. Since joining Takeda, Ms. Duprey has implemented a transformation of HR in the U.S., including a new operating model, structure, capabilities and technology. In addition, she built a new diversity, equity and inclusion (DE&I) organization which has shaped a leading-edge DE&I strategy for Takeda in the U.S. Prior to joining Takeda, Ms. Duprey served as Head of HR, U.S. Organization & Worldwide Medical at Biogen where she developed and drove the talent and organization strategy and served as a trusted advisor in regards to key business, talent and organizational decisions. She has held various HR roles at companies such as General Electric and began her career in management consulting at Clarion Healthcare focused on biopharma commercialization. Ms. Duprey holds a bachelor's degree in biology from Harvard University and an MBA from Massachusetts Institute of Technology (MIT) Sloan School of Management.

Name (Date of birth)	Responsibilities and status within Takeda	Business experience
Milano Furuta (February 26, 1978)	President, Japan Pharma Business Unit	Milano Furuta is President, Japan Pharma Business Unit of Takeda Pharmaceutical Company Limited. Mr. Furuta joined Takeda in 2010 and has worked on various projects in corporate strategy, corporate development, and post-merger integration in Japan and Switzerland. He managed the Diabetes Business Unit in Mexico and served as General Manager in Sweden. He went on to serve as Corporate Strategy Officer and Chief of Staff in Japan for two years before his appointment to his current role. Prior to joining Takeda, Mr. Furuta worked as an equity research analyst at an investment management firm in the United States. He began his career in banking and private equity investment in Japan, where he was involved with several types of financial transactions, including leveraged buyouts and debt restructuring. Mr. Furuta holds an MBA from The Wharton School, University of Pennsylvania and a BA in international affairs from Hitotsubashi University, Japan.
Takako Ohyabu (August 26, 1979)	Chief Global Corporate Affairs & Sustainability Officer	Takako Ohyabu is Chief Global Corporate Affairs & Sustainability Officer overseeing corporate communications, corporate social responsibility, public affairs, global security and crisis management, and corporate sustainability for Takeda Pharmaceutical Company Limited. She joined the company in November 2019 as Chief Communications and Public Affairs Officer Designate. Prior to joining Takeda, Ms. Ohyabu led Global Corporate Communications function at Nissan Motor Corporation. Before that she was with General Electric Company managing corporate communications for a variety of industries and building the corporate brand in both developed and emerging markets. Ms. Ohyabu holds a master's degree in Public Administration from Columbia University's School of International and Public Affairs and a bachelor's degree in Political Science from the International Christian University in Japan.
Julie Kim (June 6, 1970)	President, U.S. Business Unit and U.S. Country Head	Julie Kim is President of Takeda's U.S. Business Unit and U.S. Country Head. Ms. Kim has nearly 30 years of experience in health care, 15 of those in international leadership positions. She joined Takeda in 2019 through the acquisition of Shire, where throughout her time she held many diverse roles with increasing responsibility through her time at Baxter/Baxalta/Shire. These included roles as Global Franchise Head in different therapy areas, international market access, country and regional general management, marketing, and emerging market development. Ms. Kim represents Takeda as a Global Board Member of the Plasma Protein Therapeutics Association, currently serving as Treasurer. She is also a member of the Board of Directors of Croda International Plc., a company that uses smart science to create high performance ingredients and technologies that improve lives. Prior to joining the biopharmaceutical industry, Ms. Kim worked in health care consulting in the U.S. Ms. Kim holds an MBA from the J. L. Kellogg Graduate School of Management at Northwestern University and a BA in Economics from Dartmouth College. Ms. Kim was also a 2013 Healthcare Businesswomen's Association Rising Star.

Name (Date of birth)	Responsibilities and status within Takeda	Business experience
Mwana Lugogo (January 30, 1970)	Chief Ethics and Compliance Officer	Mwana Lugogo is Chief Ethics & Compliance Officer of Takeda Pharmaceutical Company Limited. She joined the company in 2012 to establish the Compliance function for Growth & Emerging Market Business Unit, and was appointed to lead the newly-created Global Ethics & Compliance organization in 2015. In January 2019, she joined the Takeda Executive Team. Ms. Lugogo is passionate about strengthening ethics-based culture and bringing Takeda's values to life, as part of our commitment to patients, to each other and to society. Ms. Lugogo is an International Studies graduate of Virginia Polytechnic Institute & State University. She has a Juris Doctorate from Harvard Law School, and a Master's in Public Policy from Harvard's John F. Kennedy School of Government.
Yoshihiro Nakagawa (July 26, 1960)	Global General Counsel	Yoshihiro Nakagawa is Corporate Officer and Global General Counsel of Takeda Pharmaceutical Company Limited. Mr. Nakagawa joined the company in 1983, serving in a variety of roles including Company Secretary of Takeda Europe Holdings in London and Senior Vice President of Takeda Legal Department, prior to his 2014 appointment as Corporate Officer and Global General Counsel. Mr. Nakagawa received a law degree from Kobe University in Japan.
Giles Platford (April 26, 1978)	President, Plasma-Derived Therapies Business Unit	Giles Platford is President, Plasma-Derived Therapies Business Unit at Takeda Pharmaceutical Company Limited. Mr. Platford joined Takeda in 2009 as General Manager of Brazil, after which he assumed the role of Area Head for Middle East, Turkey & Africa, before then joining Takeda Executive Team in 2014 as President of Emerging Markets. In 2017 he took up his most recent role as President of Europe & Canada, where he also represented Takeda as a board member of the European Federation of Pharmaceutical Industries and Associations (EFPIA). Prior to joining Takeda, Mr. Platford spent eight years in Asia Pacific, where he held a number of roles of increasing responsibility in Business Development, Commercial and General Management. Mr. Platford holds a Bachelor of Arts degree in business and marketing management from Oxford Brookes University, UK, and is currently based in Boston, USA.
Gabriele Ricci (October 18, 1978)	Chief Data and Technology Officer	Gabriele Ricci is Chief Data and Technology Officer (CDTO) of Takeda Pharmaceutical Company Limited. He was appointed to this role in February 2022 and leads the transformation of Takeda's Data, Digital and Technology division. Mr. Ricci joined Takeda in 2019 as Head of Plasma-Derived Therapies (PDT) IT, during which he drove initiatives to meet the large and growing demand for plasma-derived products, with highly specialized services that require strategic capacity, innovative business models, dedicated R&D and agile supply allocation on a global scale. Prior to joining Takeda, Mr. Ricci served as Head of Digital Health and Emerging Technology at Shire, where he leveraged new and emerging technologies to optimize internal operations and deliver differentiated patient and customer experiences. Mr. Ricci has also served as Shire's Head of Technical Operations IT and held leadership positions at Novartis, Johnson & Johnson and Bristol-Myers Squibb. Mr. Ricci brings more than 20 years of information technology and engineering expertise in the life sciences industry and sits on several advisory boards for non-profit organizations focused on digital, life sciences and manufacturing. Mr. Ricci holds an MBA from the MIB Trieste School of Management and a bachelor's degree in Engineering from the University of Rome Tor Vergata.

Name (Date of birth)	Responsibilities and status within Takeda	Business experience
Koki Sato (December 10, 1980)	Corporate Strategy Officer	Koki Sato is Corporate Strategy Officer of Takeda Pharmaceutical Company Limited. Mr. Sato joined Takeda in 2003 and has been increasing responsibilities throughout his career with Takeda spanning many countries and multiple functions. After he took a regional role in Emerging Markets in 2012, he has since held several leadership roles, such as country manager of Belarus, general manager of Ukraine cluster and general manager of India before taking his current role. Mr. Sato holds a bachelor's degree in economics from School of Political Science & Economics at Waseda University in Tokyo.
Ramona Sequeira (November 21, 1965)	President, Global Portfolio Division	Ramona Sequeira is a member of Takeda Executive Team and President of Takeda's Global Portfolio Division where she leads Takeda's Regional Business Units across Europe and Canada, Growth and Emerging Markets, and China – as well as Takeda's Global Vaccine Business Unit and Global Medical and Global Product and Launch Strategy Functions. Her focus for the division is to accelerate growth, support public health and improve health equity by increasing the impact of Takeda's transformational medicines and vaccines for people worldwide. Ms. Sequeira joined Takeda in 2015. For more than 25 years in the biopharmaceutical industry, she has led businesses across multiple markets, cultures and healthcare systems. She has lived and worked in Canada, Europe, and the U.S. for Takeda and, prior to that, for Eli Lilly. Her first commitment has always been to drive strategies around meeting the needs of patients, while also prioritizing sustainable growth, high employee engagement and strong organizational alignment. Ms. Sequeira spent seven years as a member of PhRMA's Board of Directors, serving on numerous committees, as treasurer, vice-chair and most recently as the first woman to serve as chair in the organization's history. As chair, she focused on the industry's role in shaping a positive environment that rewards pharmaceutical innovation and ensures patients have access to life transforming treatments and vaccines. Ms. Sequeira is a member of the Board of Directors of Edwards Life Sciences. Ms. Sequeira holds an MBA from McMaster University in Canada and a Bachelor of Science degree with honours in molecular genetics and molecular biology from the University of Toronto.
Thomas Wozniewski, Ph.D. (July 26, 1962)	Global Manufacturing and Supply Officer	Thomas Wozniewski is Global Manufacturing & Supply Officer of Takeda Pharmaceutical Company Limited. He was appointed to this role in July 2014. Dr. Wozniewski has focused on the globalization, the technological and digital transformation and the implementation of a continuous improvement culture within the manufacturing network of 31 manufacturing sites. Dr. Wozniewski has more than 20 years of experience in the pharmaceutical industry. Prior to joining Takeda, Dr. Wozniewski held senior leadership roles in Manufacturing, Quality and Supply Chain Management at Bayer Consumer Care Switzerland, Bayer Healthcare AG, Schering AG and Boehringer Ingelheim in Germany. Dr. Wozniewski holds a doctorate degree in pharmaceutical biology from the University of Regensburg, Germany.

B. Compensation

The following table provides information about our Internal Directors' compensation on an individual basis in the fiscal year ended March 31, 2023.

Name (Position)	Total consolidated compensation (millions of yen)	Company	Amount of consolidated compensation by type (millions of yen)				
			Basic compensation	Performance-based compensation: Annual bonus	Performance-based compensation: Performance Share Unit awards[1]	Performance-based compensation: Restricted Stock Unit awards[1]	Other
Christophe Weber (Director)	¥ 1,723	Takeda Pharmaceutical Company Limited	¥ 230[3]	¥ 181	¥ 688[4]	¥ 463[4]	¥ —
		Takeda Pharmaceuticals U.S.A., Inc.[2]	65	96	—	—	—
Masato Iwasaki (Director)[5]	243	Takeda Pharmaceutical Company Limited	66	38	85[6]	53[6]	—
Andrew S. Plump (Director)	973	Takeda Pharmaceutical Company Limited	12	—	—	—	—
		Takeda Pharmaceuticals International, Inc. and Takeda Development Center Americas, Inc.[7]	157	196	349[8]	215[8]	43[9]
Costa Saroukos (Director)	691	Takeda Pharmaceutical Company Limited	215[10]	141	199[11]	135[11]	—

Notes:

(1) Compensation expense related to Performance Share Unit awards and Restricted Stock Unit awards are recognized over multiple fiscal years, depending on the length of the period eligible for earning compensation. This column shows amounts recognized as expenses during the fiscal year ended March 31, 2023.

(2) Shows the salary and annual bonus earned as Head of Global Business of Takeda Pharmaceuticals U.S.A., Inc.

(3) Basic compensation includes the grossed-up amount paid for residence and pension allowances etc. for the relevant officer (100 million JPY).

(4) The amount recognized as an expense during the fiscal year for the stock incentive plan (Board Incentive Plan) grants awarded in fiscal years 2019-2022.

(5) Masato Iwasaki retired at the close of 147th General Meeting of Shareholders held on June 28, 2023.

(6) The amount recognized as an expense during the fiscal year for the stock incentive plan (Board Incentive Plan) grants awarded in fiscal years 2019-2022.

(7) Shows the salary and other amounts earned as the President, Research and Development of Takeda Development Center Americas, Inc.

(8) The amount recognized as an expense during the fiscal year for the stock incentive plan (Employee Stock Ownership Plan and the Long Term Incentive Plan for Company Group Employees Overseas (LTIP)) grants awarded in fiscal years 2019-2022.

(9) Amounts of local retirement plan contributions and other additional benefits paid by Development of Takeda Development Center Americas, Inc. during the fiscal year, as well as the amount equal to taxes on such amounts.

(10) Basic compensation includes the grossed-up amount paid for residence, pension allowances, and educational allowances etc. for the relevant officer (94 million JPY).

(11) The amount recognized as an expense during the fiscal year for the stock incentive plan (Board Incentive Plan) grants awarded in fiscal years 2019-2022.

The following table provides information about our External Directors' compensation on an individual basis in the fiscal year ended March 31, 2023.

Name (Position)[1]	Total consolidated compensation (millions of yen)	Company	Amount of consolidated compensation by type (millions of yen)				
			Basic compensation	Performance-based compensation		Restricted Stock Unit awards[2]	Other
				Annual bonus	Performance Share Unit awards		
Masami Iijima (Director)	¥ 43	Takeda Pharmaceutical Company Limited	¥ 24	¥ —	¥ —	¥ 19	¥ —
Olivier Bohuon (Director)	38	Takeda Pharmaceutical Company Limited	19	—	—	19	—
Jean-Luc Butel (Director)	38	Takeda Pharmaceutical Company Limited	19	—	—	19	—
Ian Clark (Director)	38	Takeda Pharmaceutical Company Limited	19	—	—	19	—
Steven Gillis (Director)	38	Takeda Pharmaceutical Company Limited	19	—	—	19	—
John Maraganore[3] (Director)	32	Takeda Pharmaceutical Company Limited	16	—	—	16	—
Michel Orsinger (Director)	39	Takeda Pharmaceutical Company Limited	20	—	—	19	—
Koji Hatsukawa (Director who is an Audit and Supervisory Committee Member)	43	Takeda Pharmaceutical Company Limited	24	—	—	19	—
Yoshiaki Fujimori (Director who is an Audit and Supervisory Committee Member)	41	Takeda Pharmaceutical Company Limited	22	—	—	19	—
Emiko Higashi (Director who is an Audit and Supervisory Committee Member)	43	Takeda Pharmaceutical Company Limited	24	—	—	19	—
Kimberly A. Reed[3] (Director who is an Audit and Supervisory Committee Member)	34	Takeda Pharmaceutical Company Limited	18	—	—	16	—
Masahiro Sakane[4] (Director)	10	Takeda Pharmaceutical Company Limited	6	—	—	3	—
Shiro Kuniya[4] (Director)	8	Takeda Pharmaceutical Company Limited	5	—	—	3	—
Toshiyuki Shiga[4] (Director)	8	Takeda Pharmaceutical Company Limited	5	—	—	3	—

Notes:

(1) As for Directors who were transferred between Directors who are not Audit and Supervisory Committee members and Directors who are Audit and Supervisory Committee members during this fiscal year, the Director titles represent when the Directors were selected at the 146th Ordinary General Meeting of Shareholders held on June 29, 2022.

(2) Compensation expense related to Restricted Stock Unit awards are recognized over multiple fiscal years, depending on the length of the period eligible for earning compensation. This column shows amounts recognized as expenses during the fiscal year ended March 31, 2023.

(3) John Maraganore and Kimberly A. Reed were newly elected and took office at the 146th Ordinary General Meeting of Shareholders held on June 29, 2022.

(4) Masahiro Sakane, Shiro Kuniya, and Toshiyuki Shiga retired at the close of 146th General Meeting of Shareholders held on June 29, 2022.

Share-based Compensation Payments

We maintain certain share-based compensation payment plans for the benefit of our directors and certain of our employees. In the fiscal years ended March 31, 2021, 2022 and 2023, we recorded total compensation expense related to our share-based payment plans of 39.4 billion JPY, 43.7 billion JPY and 61.0 billion JPY, respectively, in our consolidated statements of profit or loss. For detailed information about our share-based compensation plans, including our stock option plan, stock incentive plan, phantom stock appreciation rights and restricted stock units, see Note 28 to our audited consolidated financial statements.

C. Board Practices

See "—A. Directors and Senior Management." for information about the terms of service of the members of our Board of Directors and the committees thereof.

Corporate Governance Structure

Under the Companies Act, joint stock corporations in Japan may adopt a corporate governance structure comprised of a board of directors and an audit and supervisory committee, commonly referred to as the audit and supervisory committee system, in lieu of the traditional structure comprised of a board of directors and a board of corporate auditors or the alternative structure comprised of a board of directors and three statutory committees. The members of the audit and supervisory committee consist of three or more directors. We adopted the audit and supervisory committee system in June 2016, in order to increase transparency and independence of our board of directors, and further enhance our corporate governance, by establishing the systems of audit and supervision conducted by the Audit and Supervisory Committee and increasing the proportion of the number of External Directors and the diversity of our board of directors. This governance structure also enables us to enhance the separation of business execution and supervision by delegating certain decision-making authority to individual members of our board of directors, realizing increased agility in decision-making and helping the board of directors focus more on discussions of business strategies and particularly important business matters.

Board of Directors

Pursuant to the audit and supervisory committee system, our board of directors is comprised of directors who are Audit and Supervisory Committee members and directors who are not. Our articles of incorporation provide for a board of directors consisting of no more than 12 members who are not Audit and Supervisory Committee members and no more than four directors who are Audit and Supervisory Committee members. All directors are elected by our shareholders at a general meeting of shareholders, with directors who are Audit and Supervisory Committee members elected separately from other directors. The term of office for directors who are not Audit and Supervisory Committee members expires at the close of the ordinary general meeting of shareholders held with respect to the last fiscal year ending within one year after their election, and the term of office for directors who are Audit and Supervisory Committee members expires at the close of the ordinary general meeting of shareholders held with respect to the last fiscal year ending within two years after their election. The current terms of our directors are set forth under "Item 6. Directors, Senior Management and Employees—A. Directors and Senior Management." All directors may serve any number of consecutive terms. Except as described below, none of our directors have entered service contracts with us or any of our subsidiaries providing for benefits upon termination of employment.

Upon a termination by the relevant company, other than for cause, or the voluntary termination by the relevant director for good reason of his appointment as director or employment relationship, in each case as defined in the relevant agreement, and subject to the other conditions contained in such agreement, the following directors will be entitled to the severance payments or other benefits described below. The payments and benefits described below are in addition to any accrued and unpaid amounts that may be owed to the relevant director at the time of such termination.

Name	Company	Severance Payment	Other Benefits
Christophe Weber	Takeda	Sum of (i) 100% of annual basic compensation, (ii) 100% of annual target bonus and (iii) 100% of annual target value of Long-Term Incentive payments, subject to the approval of the shareholders' meeting, to the extent required by applicable law and to the extent permitted in light of fiduciary duty and the duty of loyalty of the directors of Takeda	Certain repatriation-related benefits, subject to the approval of the shareholders' meeting, to the extent required by applicable law and to the extent permitted in light of fiduciary duty and the duty of loyalty of the directors of Takeda
	Takeda Pharmaceuticals U.S.A., Inc.	Sum of (i) 100% of annual base salary and (ii) 100% of annual target value of Short-Term Incentive payments, subject to the approval of the shareholders' meeting, to the extent required by applicable law and to the extent permitted in light of fiduciary duty and the duty of loyalty of the directors of Takeda	None

Costa Saroukos	Takeda	Sum of (i) 100% of annual basic compensation, (ii) 100% of annual target bonus and (iii) 100% of annual target value of Long-Term Incentive payments, subject to the approval of the shareholders' meeting, to the extent required by applicable law and to the extent permitted in light of fiduciary duty and the duty of loyalty of the directors of Takeda	Certain repatriation-related benefits, subject to the approval of the shareholders' meeting, to the extent required by applicable law and to the extent permitted in light of fiduciary duty and the duty of loyalty of the directors of Takeda
Andrew S. Plump	Takeda Pharmaceuticals International, Inc.	Sum of (i) 12 months of current monthly base salary (24 months in the case where Mr. Plump voluntarily terminates his employment for good reason) and (ii) 100% of annual target level bonus under the Short-Term Incentive Program	Certain health insurance benefits

Our board of directors has the ultimate responsibility for the administration of our affairs. Our board of directors, however, may delegate by its resolution some or all of its decision-making authority in respect of the execution of operational matters (excluding certain matters specified in the Companies Act) to individual directors and has delegated such decision-making authority as described below. Our board of directors elect one or more representative directors from among its members who are not Audit and Supervisory Committee members. Each of the representative directors has the authority to represent us in the conduct of our affairs.

We entered into indemnity agreements with each of Takeda's directors for liability arising from their status as directors or out of an alleged wrongful act by them in such capacity to the extent permitted by applicable law.

Audit and Supervisory Committee

Our directors who are Audit and Supervisory Committee members are not required to be certified public accountants. They may not serve concurrently as executive directors, managers or any other type of employee for us or for any of our subsidiaries, or as accounting advisors or corporate executive officers for any of our subsidiaries. In addition, more than half of our directors who are Audit and Supervisory Committee members at any one time must be external directors as defined under the Companies Act, who have not served as executive directors, corporate executive officers, managers or any other type of employee for us or any of our subsidiaries for ten years prior to their election and fulfill certain other requirements specified in the Companies Act.

The Audit and Supervisory Committee has a statutory duty to audit the administration of our affairs by our directors, to examine the financial statements and business reports to be submitted to the shareholders by a representative director, to prepare an audit report each year, to determine details of proposals concerning the appointment and dismissal of independent auditors and the refusal to reappoint independent auditors for submission to general meetings of shareholders and to determine the opinion on election, removal, resignation of or compensation for directors who are not Audit and Supervisory Committee members, which may be expressed at a general meeting of shareholders. An Audit and Supervisory Committee member may note his or her opinion in the audit report issued by the Audit and Supervisory Committee if such an opinion differs from that expressed in the audit report. Additionally, our Audit and Supervisory Committee serves as our "audit committee" for the purposes of Rule 10A-3 under the Exchange Act. We are required to appoint and have appointed an independent auditor, who has a statutory duty of examining the financial statements to be submitted to the shareholders by a Representative Director and preparing its audit report thereon. KPMG AZSA LLC currently acts as our independent auditor.

As of the date of this annual report, Mr. Koji Hatsukawa, Mr. Yoshiaki Fujimori, Ms. Emiko Higashi and Ms. Kimberly A. Reed are appointed as the Audit and Supervisory Committee members.

Takeda Executive Team

As management tasks continue to diversify, we have established a Takeda executive team under the President and Chief Executive Officer, consisting of certain directors and employees in senior positions who manage and supervise our key functions. Takeda executive team participates in Business and Sustainability Committee, which is responsible for corporate / business development matters and corporate sustainability-related matters, a Portfolio Review Committee, which is responsible for R&D and products-related matters, and a Risk, Ethics and Compliance Committee, which is responsible for internal audit, risk management and compliance matters. Our board of directors has delegated all of its decision-making authority in respect of operational matters (excluding certain matters specified in the Companies Act, as well as substantive matters valued at 100 billion JPY or more or those matters which will have substantial impact on us or our stakeholders) to the President and Chief Executive Officer, three directors belonging to the Business and Sustainability Committee, two directors belonging to the Portfolio Review Committee, and two directors belonging to the Risk, Ethics and Compliance Committee.

Nomination Committee and Compensation Committee

We also have voluntarily established a Nomination Committee and a Compensation Committee as advisory committees of the board of directors. All members of each Committee must be External Directors. Furthermore, at least one director who is an Audit and Supervisory Committee member must be assigned to each committee and each committee must be chaired by an external director. As of the date of this annual report, the Nomination Committee consists of one external director who serves as chairperson, and four other external directors. One other director who is not an external director attends the Nomination Committee as observer. The Compensation Committee consists of one external director who serves as chairperson, and three other external directors. Together, the committees serve to ensure transparency and objectivity in decision-making relating to personnel matters for directors (including appropriate standards and procedures for appointment and reappointment and establishing and administering appropriate succession plans) and the compensation system (including appropriate levels of compensation for the directors, appropriate performance targets within the bonus system for directors and appropriate bonuses based on business results). Also, by resolution of the board of directors, the authority to decide the amount of individual remuneration of Internal Directors who are not Audit and Supervisory Committee members is delegated to the Compensation Committee, through which we have realized a more transparent process in determining individual remuneration.

As of the date of this annual report, Mr. Masami Iijima, Mr. Jean-Luc Butel, Mr. Steven Gillis, Mr. Michel Orsinger and Mr. Yoshiaki Fujimori are appointed as the Nomination Committee members and Ms. Emiko Higashi, Mr. Olivier Bohuon, Mr. Ian Clark and Mr. Michel Orsinger are appointed as the Compensation Committee members.

Limitation of Liability of Directors

Under the Companies Act and our articles of incorporation, we may exempt, by resolution of the board of directors, our directors from liabilities to us arising in connection with their failure to execute their duties in good faith and without gross negligence, within the limits stipulated by applicable laws and regulations. In addition, our articles of incorporation provide that we may enter into agreements with our directors (excluding executive directors as defined under the Companies Act) to limit their respective liabilities to us arising from their failure to execute their duties in good faith and without gross negligence, subject to applicable laws and regulations.

D. Employees

As of March 31, 2021, 2022 and 2023, we had 47,099, 47,347 and 49,095 employees on a consolidated basis, respectively. These numbers of employees represent the number of permanent employees excluding temporary employees and were calculated on a full-time equivalent basis. The following table shows our employees by geographic locations as of March 31, 2023.

Japan	United States	Europe and Canada	Other	Total
5,732	21,192	14,528	7,643	49,095

We have concluded a collective bargaining agreement with the Takeda Pharmaceutical Workers Union, through which we have established sound relations with our employees in Japan. We hold regular dialogues with the union concerning, among other issues, conditions of employment and human resources practices. Similarly, all of our group companies hold discussions with their respective workers unions and employee representatives in accordance with local laws. We have an employee stock ownership association for employees of Takeda.

E. Share Ownership

The following table shows the number of shares as of March 31, 2023 owned by directors of the Company as of the date of this annual report.

Directors

Name	Number of shares held (Number of shares to be provided)[1]	Number of ADSs held (Number of ADSs to be provided)[2]
Christophe Weber	628,100	—
	(817,138)	(—)
Andrew Plump	—	111,097
	(—)	(701,712)
Costa Saroukos	—	—
	(230,749)	(—)
Masami Iijima	—	—
	(10,270)	(—)
Olivier Bohuon	—	1,300
	(17,738)	(—)
Jean-Luc Butel	—	—
	(21,914)	(—)
Ian Clark	—	2,096
	(17,738)	(—)
Steven Gillis	—	8,257
	(17,738)	(—)
John Maraganore	—	—
	(5,121)	(—)
Michel Orsinger	—	—
	(21,914)	(—)
Miki Tsusaka	—	—
	(—)	(—)
Koji Hatsukawa	6,400	—
	(19,900)	(—)
Yoshiaki Fujimori	9,000	—
	(19,900)	(—)
Emiko Higashi	—	—
	(21,914)	(—)
Kimberly A. Reed	—	9,353
	(5,121)	(—)
Total	643,500	132,103
	(1,227,155)	(701,712)

Notes:

(1) The number of shares held represents the number of ordinary shares held as of March 31, 2023. The number of shares to be provided includes the number of ordinary shares vested but undelivered and scheduled to be vested, including those granted to directors based outside of Japan that will be converted to ADSs for settlement following vesting, under the Board Incentive Plan ("BIP").

(2) The number of ADSs held represents the number of American Depositary Shares held as of March 31, 2023 and is rounded to the nearest whole number. Each ADS represents one half of an ordinary share. The number of ADSs held by Kimberly A. Reed includes 7,978 shares held by her close family members. The number of ADSs to be provided includes the number of American Depositary Shares vested but undelivered and scheduled to be vested under Long-Term Incentive Plan for Company Group Employees Overseas ("LTIP").

Each of our directors held less than one percent of our total issued shares as of March 31, 2023. Shares held by directors have equal voting rights as common stock held by other holders.

The number of shares to be provided pursuant to the BIP is comprised of Restricted Stock Unit awards ("RSU awards") and Performance Share Unit awards ("PSU awards"). RSU awards vest one third each year over a three-year period and PSU awards vest three years from the date of grant. Included PSU awards to be vested in the future years represent the total number of shares to be issued assuming that relevant targets are met at the 100% level; the actual number of shares issued may be fewer or greater depending on the level at which targets are met.

The number of ADSs to be provided pursuant to the LTIP is comprised of RSU awards and Performance Stock Unit awards ("PSU awards"). RSU awards vest one third each year over a three-year period and PSU awards vest three years from the date of grant. Included PSU awards to be vested in the future years represent the total number of ADSs to be issued assuming that relevant targets are met at the 100% level; the actual number of ADSs issued may be fewer or greater depending on the level at which targets are met.

For detailed information about our share-based compensation plans, including BIP and LTIP, see Note 28 to our audited consolidated financial statements.

F. Disclosure of a Registrant's Action to Recover Erroneously Awarded Compensation

Not applicable.

Item 7. Major Shareholders and Related Party Transactions

A. Major Shareholders

The following table sets forth the number of shares held of record by each of our principal shareholders as well as the percentage of our issued shares held by each of our principal shareholders as of March 31, 2023.

Shareholder	Number of shares held of record	Percentage of issued shares[(1)]
	(thousands, except percentages)	
The Master Trust Bank of Japan, Ltd. (Trust account)	261,558	16.76 %
Custody Bank of Japan, Ltd. (Trust account)	87,646	5.62
The Bank of New York Mellon as depositary bank for depositary receipt holders (Standing proxy: Sumitomo Mitsui Banking Corporation)	69,832	4.47
JP Morgan Chase Bank 385632 (Standing proxy: Settlement & Clearing Services Department, Mizuho Bank, Ltd.)	58,526	3.75
State Street Bank West Client-Treaty 505234 (Standing proxy: Settlement & Clearing Services Department, Mizuho Bank, Ltd.)	28,561	1.83
Nippon Life Insurance Company (Standing proxy: The Master Trust Bank of Japan, Ltd.)	28,288	1.81
JPMorgan Securities Japan Co., Ltd.	25,622	1.64
SSBTC Client Omnibus Account (Standing proxy: The Hongkong and Shanghai Banking Corporation Limited Tokyo Branch	21,860	1.40
JP Morgan Chase Bank 385781 (Standing proxy: Settlement & Clearing Services Department, Mizuho Bank, Ltd.)	20,172	1.29
Takeda Science Foundation	17,912	1.15
Total	619,977	39.72 %

Note:

(1) Percentage of issued shares excludes treasury stock held as of March 31, 2023. As of March 31, 2023, we held 27,767,213 shares of common stock as treasury stock, which include 21,467,090 shares held by us, 6,214,997 shares held in trust for our stock-based compensation plans and 85,126 shares held by equity-method affiliates (based on our ownership percentage in them). The total number of issued shares, less treasury stock, used to calculate percentages in the above table include such shares held in trust or by equity-method affiliates.

Our major shareholders of common stock have the same voting rights as other holders of common stock.

According to a statement on Schedule 13G (Amendment No. 2) filed on February 3, 2023, Sumitomo Mitsui Trust Holdings, Inc. beneficially owned 93,599,534 shares of our common stock, representing 5.9% of our outstanding shares of common stock. However, we have not confirmed the status of these shareholdings as of March 31, 2023.

According to a statement on Schedule 13G (Amendment No. 4) filed on February 7, 2023, BlackRock, Inc. beneficially owned 113,749,385 shares of our common stock, representing 7.2% of our outstanding shares of common stock. However, we have not confirmed the status of these shareholdings as of March 31, 2023.

As of March 31, 2023, there were 346 holders of record of our common stock with addresses in the U.S., whose shareholdings represented approximately 18% of our outstanding common stock on that date. One such shareholder was The Bank of New York Mellon as depositary for holders of ADSs, which held 69,832 thousand shares, or 4.47% of the total number of shares in issue, as of March 31, 2023. Because some of these shares were held by brokers or other nominees, the number of holders of record with addresses in the U.S. might not fully reflect the number of beneficial owners in the U.S.

To the extent known to us, we are not directly or indirectly owned or controlled by any other corporation, by any foreign government or by any other natural or legal person severally or jointly.

To our knowledge, there are no arrangements, which may at a subsequent date result in a change in control of us.

B. Related Party Transactions

From time to time, we enter into agreements and engage in transactions with our related parties, within the meaning of Item 7.B of Form 20-F, in the ordinary course of our business. For the fiscal year ended March 31, 2023, such transactions included, but were not limited to, R&D-related services agreements, business development transactions and equity investments. The terms and conditions of our related party transactions

are consistent with third-party transactions and reflect market prices. Takeda does not consider the amounts involved in these transactions to be material to its business.

C. Interests of Experts and Counsel

Not applicable.

Item 8. Financial Information

A. Consolidated Statements and Other Financial Information

Our audited consolidated financial statements are included under “Item 18—Financial Statements.”

Legal Proceedings

The information required by this item is set forth in our consolidated financial statements included in this annual report. See Note 32 to our audited consolidated financial statements for a detailed discussion of legal proceedings.

Dividends

Takeda’s policy on the allocation of capital is as follows:

- Invest in growth drivers; and
- Shareholder returns.

In respect of "Invest in growth drivers", Takeda makes strategic investments in internal and external opportunities to enhance the pipeline, new product launches, and plasma-derived therapies. With regard to "Shareholder returns", Takeda has adopted a progressive dividend policy of increasing or maintaining the annual dividend per share each year, alongside share buybacks when appropriate.

As noted above, the return of capital to shareholders is one of the focus areas for our management, and we believe our dividend policy is an important tool for accomplishing our goals.

The following table sets forth the dividends paid with respect to each of our fiscal years indicated.

Dividends declared and paid	JPY (billions) Total dividends	Dividends per share JPY	Record date	Effective date
April 1, 2020, to March 31, 2021				
Q1 2020	¥ 141.9	¥ 90.00	March 31, 2020	June 25, 2020
Q3 2020	141.9	90.00	September 30, 2020	December 1, 2020
April 1, 2021, to March 31, 2022				
Q1 2021	141.9	90.00	March 31, 2021	June 30, 2021
Q3 2021	142.4	90.00	September 30, 2021	December 1, 2021
April 1, 2022, to March 31, 2023				
Q1 2022	140.4	90.00	March 31, 2022	June 30, 2022
Q3 2022	140.5	90.00	September 30, 2022	December 1, 2022

Dividend declared for which the effective date falls in the following fiscal year are as follows:

Dividends declared	JPY (billions) Total dividends	Dividends per share JPY	Record date	Effective date
April 1, 2023, to March 31, 2024				
Q1 2023	¥ 140.5	¥ 90.00	March 31, 2023	June 29, 2023

B. Significant Changes

No significant change has occurred since the date of the annual financial statements.

Item 9. The Offer and Listing

A. Offer and Listing Details

See Item 9.C of this annual report.

B. Plan of Distribution

Not applicable.

C. Markets

In Japan, our common stock has been listed since 1949 on the Tokyo Stock Exchange. Our common stock is also listed on the Nagoya Stock Exchange, the Fukuoka Stock Exchange and the Sapporo Securities Exchange. On each of these markets, our common stock trades under the securities identification code “4502.”

ADSs, each representing 0.5 shares of our common stock, have been listed on the New York Stock Exchange since 2018 and trade under the symbol “TAK.”

D. Selling Shareholders

Not applicable.

E. Dilution

Not applicable.

F. Expenses of the Issue

Not applicable.

Item 10. Additional Information

A. Share Capital

Not applicable.

B. Memorandum and Articles of Association

We are a joint-stock corporation incorporated in Japan under the Companies Act. The rights of our shareholders are represented by shares of our common stock as described below, and shareholders' liability is limited to the amount of subscription for such shares. As of March 31, 2023, our authorized share capital consisted of 3,500,000,000 shares of common stock of which 1,582,296,025 shares were issued.

Only the holders of our common stock will be entitled to the shareholder rights described below. In order to exercise the rights described below, holders of our ADSs will be required to withdraw their ADSs in favor of shares of our common stock in order to exercise their rights as shareholders. Additional information about the rights of ADSs is available in Exhibit 2.2.

Article 3 of our Articles of Incorporation, which are included as an exhibit hereto, set forth our objects and purposes, which are to engage in the following businesses:

- Manufacture, purchase and sale of medicines, chemicals for non-medicinal uses, quasi-medicines, medical instruments, appliances and supplies, measuring equipment, cosmetics, food products, beverages, food additives, livestock feed additives and other chemical products, and instruments, appliances and equipment relating to any of the foregoing products;
- Computerized information processing services, development, purchase and sale of software, and information providing services;
- Support of businesses, and advice, training and assistance for management;
- Trucking and freight forwarding;
- Warehousing;
- Publishing;
- Management, purchase, sale and lease of real estate; and
- Business ancillary or related to any of those specified in each foregoing clause.

Book-Entry Transfer System

The Japanese book-entry transfer system for listed shares of Japanese companies under the Book-Entry Act of Japan (the "Book-Entry Act") applies to the shares of our common stock. Under this system, shares of all Japanese companies listed on any Japanese stock exchange are dematerialized. Under the book-entry transfer system, in order for any person to hold, sell or otherwise dispose of listed shares of Japanese companies, they must have an account at an account management institution unless such person has an account at Japan Securities Depository Center, Incorporated (the "JASDEC"). "Account management institutions" are financial instruments business operators (i.e., securities firms), banks, trust companies and certain other financial institutions that meet the requirements prescribed by the Book-Entry Act, and only those financial institutions that meet the further stringent requirements of the Book-Entry Act can open accounts directly at JASDEC.

The following description of the book-entry transfer system assumes that the relevant person has no account at JASDEC.

Under the Book-Entry Act, any transfer of shares is affected through book-entry, and the title to the shares passes to the transferee at the time when the transferred number of shares is recorded in the transferee's account at an account management institution. The holder of an account at an account management institution is presumed to be the legal owner of the shares held in such account.

Under the Companies Act, in order to assert shareholders' rights against us, the transferee must have its name and address registered in the register of our shareholders, except in limited circumstances. Under the book-entry transfer system, such registration is generally made upon receipt of an all shareholders notice (*soukabunushi tsuchi*) (as described in "— Register of Shareholders") from JASDEC. For this purpose, shareholders are required to file their names and addresses with our transfer agent through the account management institution and JASDEC. See "—*Register of Shareholders*" for more information.

Non-resident shareholders are required to appoint a standing proxy in Japan or provide a mailing address in Japan. Each such shareholder must give notice of its standing proxy or a mailing address to the relevant account management institution. Such notice will be forwarded to our transfer agent through JASDEC. Japanese securities firms and commercial banks customarily act as standing proxies and provide related services for standard fees. Notices from us to non-resident shareholders are delivered to the standing proxies or mailing addresses.

Register of Shareholders

Under the book-entry transfer system, the registration of names, addresses and other information of shareholders in the register of our shareholders will be made by us upon the receipt of an all shareholders notice (with the exception that in the event of the issuance of new shares, we will register the names, addresses and other information of our shareholders in the register of our shareholders without an all shareholders notice from JASDEC) given to us by JASDEC, which will give us such an all shareholders notice based on information provided by the account management institutions. Such an all shareholders notice will be made only in cases prescribed under the Book-Entry Act such as when we fix the record date and when we make a request to JASDEC with any justifiable reason. Therefore, a shareholder may not assert shareholders' rights against us immediately after such a shareholder acquires our shares, unless such a shareholder's name and address are registered in the register of our shareholders upon our receipt of an all shareholders notice; provided, however, that, in respect of the exercise of rights of minority shareholders as defined in the Book-Entry Act, a shareholder may exercise such rights upon giving us an individual shareholder notice (*kobetsukabunushi tsuchi*) through JASDEC only during a certain period prescribed under the Book-Entry Act.

Distribution of Surplus

Under the Companies Act, the distribution of dividends takes the form of a distribution of Surplus (as defined in "—Restriction on Distribution of Surplus"), and a distribution of Surplus may be made in cash and/or in kind, with no restrictions on the timing and frequency of such distributions. The Companies Act generally requires a joint-stock corporation to make distributions of Surplus authorized by a resolution of a general meeting of shareholders. However, in accordance with the Companies Act, our Articles of Incorporation provide that the board of directors has the authority to make decisions regarding distributions of Surplus, except for limited exceptions, as provided by the Companies Act, as long as the company that has both of an independent auditor and an audit and supervisory committee satisfies the following requirements:

(a) the normal term of office of directors who are not audit and supervisory committee members expires at the close of the ordinary general meeting of shareholders held with respect to the last fiscal year ended within one year after their election (our Articles of Incorporation currently satisfies this requirement); and

(b) its non-consolidated annual financial statements and certain documents for the latest fiscal year fairly present its assets and profit or loss, as required by the ordinances of the Ministry of Justice.

A resolution of a general meeting of shareholders or the board of directors authorizing a distribution of Surplus must specify the kind and aggregate book value of the assets to be distributed, the manner of allocation of such assets to shareholders and the effective date of the distribution. If a distribution of Surplus is to be made in kind, we may, pursuant to a resolution of a general meeting of shareholders or the board of directors, grant a right to the shareholders to require us to make such distribution in cash instead of in kind. If no such right is granted to shareholders, the relevant distribution of Surplus must be approved by a special resolution of a general meeting of shareholders. See "—*Voting Rights*" for more details regarding a special resolution. Our Articles of Incorporation provide that we are relieved of our obligation to pay any distributions in cash that go unclaimed for three years after the date they first become payable.

Restrictions on the Distribution of Surplus

Under the Companies Act, we may distribute a Surplus up to the excess of the aggregate of (a) and (b) below, less the aggregate of (c) through (f) below, as of the effective date of such distribution, if our net assets are not less than 3,000,000 JPY:

(a) the amount of Surplus, as described below;

(b) in the event that extraordinary financial statements as of, or for a period from the beginning of the fiscal year to, the specified date are approved, the aggregate amount of (i) the aggregate amount as provided for by an ordinance of the Ministry of Justice as the net profit for such period described in the statement of profit and loss constituting the extraordinary financial statements, and (ii) the amount of consideration that we received for the treasury stock that we disposed of during such period;

(c) the book value of our treasury stock;

(d) in the event that we disposed of treasury stock after the end of the previous fiscal year, the amount of consideration that we received for such treasury stock;

(e) in the event described in (b) in this paragraph, the aggregate amount as provided for by an ordinance of the Ministry of Justice as the net loss for such period described in the statement of profit and loss constituting the extraordinary financial statements; and

(f) certain other amounts set forth in the ordinances of the Ministry of Justice, including (if the sum of one-half of goodwill and the deferred assets exceeds the total of share capital, additional paid-in capital and legal earnings reserve, each such amount as it appears on the balance sheet as of the end of the previous fiscal year) all or a certain part of such excess amount as calculated in accordance with the ordinances of the Ministry of Justice.

For the purposes of this section, the amount of "Surplus" is the excess of the aggregate of (I) through (IV) below, less the aggregate of (V) through (VII) below:

(I) the aggregate of other capital surplus and other retained earnings at the end of the previous fiscal year;

(II) in the event that we disposed of treasury stock after the end of the previous fiscal year, the difference between the book value of such treasury stock and the consideration that we received for such treasury stock;

(III) in the event that we reduced our share capital after the end of the previous fiscal year, the amount of such a reduction less the portion thereof that has been transferred to additional paid-in capital and/or legal earnings reserve (if any);

(IV) in the event that we reduced additional paid-in capital and/or legal earnings reserve after the end of the previous fiscal year, the amount of such a reduction less the portion thereof that has been transferred to share capital (if any);

(V) in the event that we canceled treasury stock after the end of the previous fiscal year, the book value of such treasury stock;

(VI) in the event that we distributed a Surplus after the end of the previous fiscal year, the aggregate of the following amounts:

(1) the aggregate amount of the book value of the distributed assets, excluding the book value of such assets that would be distributed to shareholders but for their exercise of the right to receive dividends in cash instead of dividends in kind;

(2) the aggregate amount of cash distributed to shareholders who exercised the right to receive dividends in cash instead of dividends in kind; and

(3) the aggregate amount of cash paid to shareholders holding fewer shares than the shares that were required in order to receive dividends in kind;

(VII) the aggregate amounts of (1) through (4) below, less (5) through (8) below:

(1) in the event that the amount of Surplus was reduced and transferred to additional paid-in capital, legal earnings reserve and/or share capital after the end of the previous fiscal year, the amount so transferred;

(2) in the event that we distributed a Surplus after the end of the previous fiscal year, the amount set aside in additional paid-in capital and/or legal earnings reserve;

(3) in the event that we disposed of treasury stock in the process of (w) a merger in which we acquired all rights and obligations of a company, (x) a corporate split in which we acquired all or a part of the rights and obligations of a split company, (y) a share exchange in which we acquired all shares of a company, or (z) a share delivery in which we acquired shares, stock acquisition rights or bonds with stock acquisition rights of a company and delivered our shares to the transferor of them as a consideration for such acquisition after the end of the previous fiscal year, the difference between the book value of such treasury stock and the consideration that we received for such treasury stock;

(4) in the event that the amount of Surplus was reduced in the process of a corporate split in which we transferred all or a part of our rights and obligations after the end of the previous fiscal year, the amount so reduced;

(5) in the event of (w) a merger in which we acquired all rights and obligations of a company, (x) a corporate split in which we acquired all or a part of the rights and obligations of a split company, (y) a share exchange in which we acquired all shares of a company, or (z) a share delivery in which we acquired shares, stock acquisition rights or bonds with stock acquisition rights of a company and delivered our shares to the transferor of them as a consideration for such acquisition after the end of the previous fiscal year, the aggregate amount of (i) the amount of other capital surplus after such merger, corporate split, share exchange or share delivery, less the amount of other capital surplus before such merger, corporate split, share exchange or share delivery, and (ii) the amount of other retained earnings after such merger, corporate split, share exchange or share delivery, less the amount of other retained earnings before such merger, corporate split, share exchange or share delivery;

(6) in the event that an obligation to cover a deficiency, such as the obligation of a person who subscribed for newly issued shares with an unfair amount to be paid in, was fulfilled after the end of the previous fiscal year, the amount of other capital surplus increased by such payment;

(7) in the event that we allotted our shares to the directors in consideration of providing service after the end of the last fiscal year, the changes in other capital surplus by such allotment; and

(8) in the event that we allotted our treasury stock to the directors in consideration of providing service and the directors transferred these stock to us for free after the end of the last fiscal year, the amount of increase in treasury stock by such transfer.

In Japan, the "ex-dividend" date and the record date for any distribution of Surplus come before the date a company determines the amount of distribution of Surplus to be paid.

For information as to Japanese taxes on dividends, see "*—Taxation — Japanese Taxation.*"

Capital and Reserves

Under the Companies Act, the paid-in amount of any newly-issued shares of stock is required to be accounted for as share capital, although we may account for an amount not exceeding one-half of such a paid-in amount as additional paid-in capital. We may generally reduce additional paid-in capital and/or legal earnings reserve by resolution of a general meeting of shareholders, subject to completion of protection procedures for creditors in accordance with the Companies Act, and, if so decided by the same resolution, we may account for the whole or any part of the amount of such reduction as share capital. We may generally reduce share capital by a special resolution of a general meeting of shareholders subject to completion of protection procedures for creditors in accordance with the Companies Act, and, if so decided by the same resolution, we may account for the whole or any part of the amount of such reduction as additional paid-in capital or legal earnings reserve.

Stock Splits

Under the Companies Act, we may at any time split shares issued into a greater number of the same class of shares by a resolution of the board of directors or by determination of an individual director to whom the authority to make such a determination has been delegated by resolution of the board of directors. A company that has issued only one class of shares may amend its articles of incorporation to increase the number of the authorized shares to be issued up to a number in proportion to the stock split by resolution of the board of directors or by determination of an individual director to whom the authority to make such determination has been delegated by resolution of the board of directors, rather than a special resolution of a general meeting of shareholders, which is otherwise required for amending the articles of incorporation. When a stock split is to be made, we must give public notice of the stock split, specifying the record date therefor, at least two weeks prior to such record date.

Under the book-entry transfer system, on the effective date of the stock split, the numbers of shares recorded in all accounts held by our shareholders at account management institutions will be increased in accordance with the applicable ratio.

Gratuitous Allocations

Under the Companies Act, we may allot any class of shares to our existing shareholders without any additional contribution by resolution of the board of directors or by determination of an individual director to whom the authority to make such determination has been delegated by resolution of the board of directors; provided that although our treasury stock may be allotted to our shareholders, any allotment of shares will not accrue to shares of our treasury stock.

When a gratuitous allocation is to be made and we set a record date therefor, we must give public notice of the gratuitous allocation, specifying the record date therefor, at least two weeks prior to the record date.

Under the book-entry transfer system, on the effective date of the gratuitous allocation, the number of shares of our common stock recorded in accounts held by our shareholders at account management institutions will be increased in accordance with a notice from us to JASDEC.

Reverse Stock Split

Under the Companies Act, we may at any time consolidate our shares into a smaller number of shares by a special resolution of the general meeting of shareholders. We must disclose the reason for the reverse stock split at the general meeting of shareholders. When a reverse stock split is to be made, we must give public notice of the reverse stock split, at least two weeks (or, in certain cases where any fractions of shares are left as a result of a reverse stock split, 20 days) prior to the effective date of the reverse stock split.

Under the book-entry transfer system, on the effective date of the reverse stock split, the numbers of shares recorded in all accounts held by our shareholders at account management institutions will be decreased in accordance with the applicable ratio.

Unit Share System

General

Our Articles of Incorporation provide that 100 shares constitute one "unit" of common stock. Our board of directors or an individual director to whom the authority to make such determination has been delegated by resolution of the board of directors is permitted to reduce the number of shares that will constitute one unit or to abolish the unit share system entirely by amending our Articles of Incorporation, without shareholders' approval, with public notice without delay after the effective date of such amendment.

Transferability of Shares Constituting Less Than One Unit

Under the book-entry transfer system, shares constituting less than one unit are transferable. Under the rules of the Japanese stock exchanges, however, shares constituting less than one unit do not comprise a trading unit, except in limited circumstances, and accordingly may not be sold on Japanese stock exchanges.

Voting Rights of a Holder of Shares Constituting Less Than One Unit

A holder of shares constituting less than one unit cannot exercise any voting rights pertaining to those shares. In calculating the quorum for various voting purposes, the aggregate number of shares constituting less than one unit will be excluded from the number of outstanding shares. A holder of shares representing one or more full units will have one vote for each full unit represented.

A holder of shares constituting less than one unit does not have any rights related to voting, such as the right to participate in a demand for the resignation of a director, the right to participate in a request for the convocation of a general meeting of shareholders and the right to join with other shareholders to propose a matter to be included in the agenda of a general meeting of shareholders.

Rights of a Holder of Shares Constituting Less Than One Unit to Require Us to Purchase Shares and to Sell Shares

Under the Companies Act, a holder of shares constituting less than one full unit may at any time request that we purchase such shares. In addition, our Articles of Incorporation provide that, pursuant to our Share Handling Regulations, a holder of shares constituting less than one full unit has the right to request that we sell to such a holder such number of shares constituting less than one full unit which, when added to the shares constituting less than one full unit currently owned by such a holder, will constitute one full unit.

Under the book-entry system, such a request must be made to us through the relevant account managing institution. The price at which shares of common stock constituting less than one unit will be purchased or sold by us pursuant to such a request will be equal to (a) the closing price of shares of our common stock reported by the Tokyo Stock Exchange on the day when the request is received by our transfer agent or (b) if no sale takes place on the Tokyo Stock Exchange on that day, the price at which the sale of shares of our common stock is executed on such stock exchange immediately thereafter.

General Meeting of Shareholders

Our ordinary general meeting of shareholders is usually held every June in Japan. The record date for an ordinary general meeting of shareholders is March 31 of each year. In addition, we may hold an extraordinary general meeting of shareholders whenever necessary by giving at least two weeks' advance notice to shareholders.

Notice of convocation of a general meeting of shareholders setting forth the time, place, purpose thereof and certain other matters set forth in the Companies Act and relevant ordinances must be mailed to each shareholder having voting rights (or, in the case of a non-resident shareholder, to his or her standing proxy or mailing address in Japan) at least two weeks prior to the date set for such a meeting. Such notice may be given to shareholders by electronic means, subject to the consent of the relevant shareholders.

The Bill for Partially Amending the Industrial Competitiveness Act of Japan has been submitted to the Diet of Japan as of May 11, 2021, which allows companies to add a provision to their Articles of Incorporation stating that a general meeting of shareholders may be held without specifying a venue, subject to confirmation by the Minister of Economy, Trade and Industry and the Minister of Justice that such companies satisfy the requirements specified by the Ordinance of the Ministry of Economy, Trade and Industry and the Ordinance of the Ministry of Justice, for falling under cases where holding a general meeting of shareholders without specifying a venue contributes to enhancing industrial competitiveness while securing the interests of shareholders.

Assuming cases where an infectious disease such as COVID-19 spreads or a natural disaster occurs and the impact thereof is ongoing or is reasonably expected to be ongoing at the time of the general meeting of shareholders, we believe that setting a venue for a general meeting of shareholders while asking shareholders to refrain from attending the venue out of consideration of shareholders' health and safety, may not always be the best option for us as the method of holding a general meeting of shareholders. Therefore, we submitted a proposal to our annual general meeting of shareholders held on June 29, 2021, which was approved by partially amending our Articles of Incorporation to the effect that we may hold a general meeting of shareholders without specifying a venue when our Board of Directors decides that, considering the interests of shareholders as

well, it is not appropriate to hold the general meeting of shareholders with a specific venue in situations such as the spread of an infectious disease or the occurrence of a natural disaster. The partial amendment of our Articles of Incorporation based on this proposal came into effect on August 5, 2021 the enactment in the Diet and the promulgation of the Act Partially Amending the Industrial Competitive Enhancement Act of Japan with the above mentioned content, and our obtaining the above mentioned confirmation by the Minister of Economy Trade and Industry and the Minister of Justice.

Any shareholder or group of shareholders holding at least 3% of the total number of voting rights for a period of six months or more may require, with an individual shareholder notice (as described in "— Register of Shareholders"), the convocation of a general meeting of shareholders for a particular purpose. Unless such a general meeting of shareholders is convened without delay or a convocation notice of a meeting which is to be held not later than eight weeks from the day such a demand is dispatched, the requiring shareholder may, upon obtaining a court approval, convene such a general meeting of shareholders.

Any shareholder or group of shareholders holding at least 300 voting rights or 1% of the total number of voting rights for a period of six months or more may propose a matter to be included in the agenda of a general meeting of shareholders, and may propose to describe such a matter together with a summary of the proposal to be submitted by such a shareholder in a convocation notice to our shareholders, by submitting a request to a director at least eight weeks prior to the date set for such a meeting (provided that we are able to limit the number of such matters proposed by each shareholder to 10), with an individual shareholder notice (as described in "— Register of Shareholders").

The Companies Act enables a company to amend its articles of incorporation in order to loosen the requirements for the number of shares held and shareholding period, as well as the period required for dispatching a convocation notice or submission of requests, all of which are required for any shareholder or group of shareholders to request the convocation of a general meeting of shareholders or to propose a matter to be included in the agenda of a general meeting of shareholders. Our Articles of Incorporation do not provide for loosening such requirements.

Voting Rights

A shareholder of record is entitled to one vote per unit (100 shares) of common stock, except that neither we nor any corporation, partnership or other similar entity in which we hold, directly or indirectly, 25% or more of the voting rights shall exercise any voting rights in respect of shares held by us or such an entity, as the case may be. Except as otherwise provided by law or by our Articles of Incorporation, a resolution can be adopted at a general meeting of shareholders by a majority of the voting rights represented at the meeting. Shareholders may also exercise their voting rights through proxies, provided that the proxy is granted to one of our shareholders having voting rights. The Companies Act and our Articles of Incorporation provide that the quorum for the election of directors is one-third of the total number of voting rights. Our Articles of Incorporation provide that the shares may not be voted cumulatively for the election of directors.

The Companies Act provides that a special resolution of the general meeting of shareholders is required for certain significant corporate transactions, including:

- any amendment to our Articles of Incorporation (except for amendments that may be made without the approval of shareholders under the Companies Act);
- a reduction of share capital, subject to certain exceptions under which a shareholders' resolution is not required, such as a reduction of share capital for the purpose of replenishing capital deficiencies;
- transfer of the whole or a part of our equity interests in any of our subsidiaries, subject to certain exceptions under which a shareholders' resolution is not required;
- a dissolution, merger or consolidation, subject to certain exceptions under which a shareholders' resolution is not required;
- the transfer of the whole or a substantial part of our business, subject to certain exceptions under which a shareholders' resolution is not required;
- the taking over of the whole of the business of any other corporation, subject to certain exceptions under which a shareholders' resolution is not required;
- a corporate split, subject to certain exceptions under which a shareholders' resolution is not required;
- a share exchange (*kabushiki kokan*) or share transfer (*kabushiki iten*) for the purpose of establishing 100% parent-subsidiary relationships, subject to certain exceptions under which a shareholders' resolution is not required;
- a share delivery (*kabushiki kofu*) for the purpose of making another corporation a subsidiary, subject to certain exceptions under which a shareholders' resolution is not required;
- any issuance of new shares or transfer of existing shares held by us as treasury stock at a "specially favorable" price and any issuance of stock acquisition rights or bonds with stock acquisition rights at a "specially favorable" price or on "specially favorable" conditions to any persons other than shareholders;
- any acquisition by us of our own shares from specific persons other than our subsidiaries;
- any reverse stock splits; or
- the removal of directors who are audit and supervisory committee members.

Except as otherwise provided by law or in our Articles of Incorporation, a special resolution of the general meeting of shareholders requires the approval of the holders of at least two-thirds of the voting rights of all shareholders present or represented at a meeting where a quorum is present. Our Articles of Incorporation provide that a quorum exists when one-third of the total number of voting rights is present or represented.

Liquidation Rights

If we are liquidated, the assets remaining after payment of all taxes, liquidation expenses and debts will be distributed among shareholders in proportion to the number of shares they hold.

Rights to Allotment of Shares

Holders of shares of our common stock have no pre-emptive rights. Authorized but unissued shares may be issued at the times and on the terms as the board of directors or an individual director to whom the authority to make such determination has been delegated by resolution of the board of directors determines, so long as the limitations with respect to the issuance of new shares at "specially favorable" prices (as described in "— Voting Rights") are observed. Our board of directors or an individual director to whom the authority to make such determination has been delegated by resolution of the board of directors may, however, determine that shareholders shall be given rights to allotment regarding a particular issue of new shares, in which case such rights must be given on uniform terms to all holders of the shares as of a record date for which not less than two weeks' prior public notice must be given. Each shareholder to whom such rights are given must also be given notice of the expiration date thereof at least two weeks prior to the date on which such rights expire. The rights to allotment of new shares may not be transferred. However, the Companies Act enables us to allot stock acquisition rights to shareholders without consideration therefor, and such stock acquisition rights are transferable. See "— Stock Acquisition Rights" below.

In cases where a particular issuance of new shares (i) violates laws and regulations or our Articles of Incorporation, or (ii) will be performed in a manner materially unfair, and shareholders may suffer disadvantages therefrom, such shareholders may file an injunction with a court of law to enjoin such issuance.

Stock Acquisition Rights

Subject to certain conditions and to the limitations on issuances at a "specially favorable" price or on "specially favorable" conditions described in "— Voting Rights," we may issue stock acquisition rights (*shinkabu yoyakuken*) and bonds with stock acquisition rights (*shinkabu yoyakuken-tsuki shasai*) by a resolution of the board of directors or by determination of an individual director to whom the authority to make such determination has been delegated by resolution of the board of directors. Holders of stock acquisition rights may exercise their rights to acquire a certain number of shares within the exercise period as set forth in the terms of their stock acquisition rights. Upon exercise of stock acquisition rights, we will be obligated either to issue the relevant number of new shares or, alternatively, to transfer the necessary number of shares of treasury stock held by us.

Record Date

The record date for annual dividends and the determination of shareholders entitled to vote at the ordinary general meeting of our shareholders is March 31. The record date for interim dividends is September 30.

In addition, by a resolution of the board of directors or by determination of an individual director to whom the authority to make such determination has been delegated by resolution of the board of directors, we may set a record date for determining the shareholders entitled to other rights and for other purposes by giving at least two weeks' prior public notice.

Under the rules of JASDEC, we are required to give notice of each record date to JASDEC promptly after setting such record date. JASDEC is required to promptly give us notice of the names and addresses of the holders of shares of our common stock, the number of shares of our common stock held by them and other relevant information as at each record date.

Purchase of Our Own Shares

Under the Companies Act and our Articles of Incorporation, we may acquire our own shares:

- by purchase on any stock exchange on which our shares are listed or by way of a tender offer, pursuant to a resolution of our board of directors subject to certain requirements;
- by purchase from a specific party other than any of our subsidiaries, pursuant to a special resolution of a general meeting of shareholders; and
- by purchase from any of our subsidiaries, pursuant to a resolution of the board of directors or determination of an individual director to whom the authority to make such determination has been delegated by resolution of the board of directors.

If we acquire our own shares from a specific party other than any of our subsidiaries as specified above at a price higher than the greater of (i) (a) the closing price of the shares at the market trading such shares on the day immediately preceding the day on which the relevant special resolution of a general meeting of shareholders is made or (b) if no sale takes place at such a market on that day, the price at which the sale of the shares is effected on such a market immediately thereafter and (ii) in the event that such shares are subject to a tender offer, the price set in the contract regarding such a tender offer on that day, shareholders may request that we include him or her as the seller of his or her shares in the proposed purchase. Any such acquisition of shares must satisfy certain requirements, such as that we may only acquire our own shares in an aggregate amount up to the amount that we may distribute as a Surplus. See "— Distribution of Surplus" above for more details regarding this amount.

Our own shares acquired by us may be held by us as treasury stock for any period or may be canceled by resolution of the board of directors or by determination of an individual director to whom the authority to make such determination has been delegated by resolution of the board of directors. We may also transfer the shares held by us to any person, subject to a resolution of the board of directors or determination of an individual director to whom the authority to make such determination has been delegated by resolution of the board of directors, and subject also to other requirements similar to those applicable to the issuance of new shares, as described in "— Rights to Allotment of Shares" above. We may also utilize our treasury stock (x) for the purpose of transfer to any person upon exercise of stock acquisition rights or (y) for the purpose of acquiring another company by way of merger, share exchange, share delivery or corporate split through exchange of treasury stock for shares or assets of the acquired company.

Request by Controlling Shareholder to Sell All Shares

Under the Companies Act and our Articles of Incorporation, in general, a shareholder holding 90% or more of our voting rights, directly or through wholly-owned subsidiaries, shall have the right to request that all other shareholders other than us (and all other holders of stock acquisition rights other than us, as the case may be) sell all shares (and all stock acquisition rights, as the case may be) held by them with our approval, which must be made by a resolution of the board of directors or by determination of an individual director to whom the authority to make such determination has been delegated by resolution of the board of directors (*kabushiki tou uriwatashi seikyu* or a "Share Sales Request"). In order to make a Share Sales Request, such a controlling shareholder will be required to issue a prior notice to us. If we approve such a Share Sales Request, we will be required to make a public notice to all holders and registered pledgees of shares (and stock acquisition rights, as the case may be) not later than 20 days before the effective date of such sales.

Sale by Us of Shares Held by Shareholders Whose Addresses Are Unknown

Under the Companies Act, we are not required to send a notice to a shareholder if notices to such shareholder fail to arrive for a continuous period of five or more years at the registered address of such a shareholder in the register of our shareholders or at the address otherwise notified to us.

In addition, we may sell or otherwise dispose of the shares held by a shareholder whose location is unknown. Generally, if

- notices to a shareholder fail to arrive for a continuous period of five or more years at the shareholder's registered address in the register of our shareholders or at the address otherwise notified to us, and
- the shareholder fails to receive distribution of Surplus on the shares for a continuous period of five or more years at the address registered in the register of our shareholders or at the address otherwise notified to us;

then we may sell or otherwise dispose of the shareholder's shares at the market price after giving at least three months' prior public and individual notices, and hold or deposit the proceeds of such sale or disposal for the shareholder.

Reporting of Substantial Shareholdings

The Financial Instruments and Exchange Law of Japan and its related regulations require any person who has become beneficially, solely or jointly, a holder of more than 5% of total issued shares of our common stock, to file with the director of a relevant local finance bureau of the Ministry of Finance within five business days a report concerning such shareholdings. With certain exceptions, a similar report must also be filed in respect of any subsequent change of 1% or more in any such holdings or any change in material matters set out in reports previously filed. For this purpose, shares of our common stock issuable to such a person upon exchange of exchangeable securities, conversion of convertible securities or exercise of warrants or stock acquisition rights (including those incorporated in bonds with stock acquisition rights) are taken into account in determining both the number of our shares held by the holder and our total issued shares.

C. Material Contracts

Acquisition of Nimbus Lakshmi, Inc.

On December 13, 2022, we entered into a share purchase agreement with Nimbus Therapeutics, LLC ("Nimbus") to acquire all of the capital stock of Nimbus Lakshmi, Inc. ("Lakshmi"), a wholly owned subsidiary of Nimbus, that owns or controls the intellectual property rights and other associated assets related to the allosteric TYK2 inhibitor known internally at Nimbus as "NDI-034858". Under the terms of the agreement, we agreed to pay Nimbus 4.0 billion USD upfront following the closing of the transaction(*), and will pay two milestone payments of 1.0 billion USD each upon achieving annual net sales of 4.0 billion USD and 5.0 billion USD of products developed from the "TAK-279" program, formally known as "NDI-034858" at Nimbus. The transaction closed on February 8, 2023. In addition, in connection with the transaction, we have agreed to assume Nimbus's obligations under a January 2022 settlement agreement with Bristol-Myers Squib and its Celgene Corporation subsidiary (collectively, "BMS") to make certain payments to BMS following the achievement of development, regulatory, and sales-based milestones for products developed from the TAK-279 program.

(*) Of the 4.0 billion USD upfront payment, 3.0 billion USD was paid in February 2023 and 0.9 billion USD was paid in April 2023. Remaining 0.1 billion USD is scheduled to be paid in August 2023.

See "Item 5.A. Operating Results—Factors Affecting Our Results of Operations *"Acquisitions"*".

Licensing and Collaboration Agreements

In the ordinary course of our business, we enter into agreements for licensing or collaboration in the development and commercialization of products. Our business does not materially depend on any one of these agreements. Instead, they form a portion of our overall strategy to leverage a mix of internal and external resources to develop and commercialize new products. Certain of the agreements which have led to successful commercialization to date are summarized in "Item 4. Information on the Company—B. Business Overview—Licensing and Collaboration." Our Licensing and Collaboration Agreement with Seagen Inc. (formerly Seattle Genetics, Inc.) is filed as an exhibit hereto to provide investors with an example of one such agreement. We believe this agreement is representative of our licensing and collaboration agreements for marketed products in that it provides for the payment of development and commercial milestone payments and sales-based royalties and sets forth the parties' responsibilities relating to the terms of co-development, co-manufacturing and co-marketing efforts, as well as providing for certain geographic limitations and limitations on term for the relevant licensing and collaboration efforts. The specific terms of each of our licensing or collaboration agreements are negotiated individually. Agreements for compounds still in development may have additional terms governing, for example, equity investments or other financial and non-financial matters.

D. Exchange Controls

The Foreign Exchange and Foreign Trade Act of Japan (*Gaikoku Kawase oyobi Gaikoku Boueki Hou*) (the "FEFTA") and related cabinet orders and ministerial ordinances, which we refer to collectively as the Foreign Exchange Regulations, govern certain aspects relating to the acquisition and holding of shares by "exchange non-residents" and by "foreign investors" (as these terms are defined below). It also applies in some cases to the acquisition and holding of ADSs representing shares of our common stock acquired and held by exchange non-residents and by foreign investors. In general, the Foreign Exchange Regulations currently in effect do not affect transactions between exchange non-residents to purchase or sell shares or ADSs outside Japan using currencies other than Japanese yen.

Exchange residents are defined in the Foreign Exchange Regulations as:

(i) individuals who reside within Japan; or

(ii) corporations whose principal offices are located within Japan.

Exchange non-residents are defined in the Foreign Exchange Regulations as:

(i) individuals who do not reside in Japan; or

(ii) corporations whose principal offices are located outside Japan.

Generally, branches and other offices of non-resident corporations located within Japan are regarded as exchange residents. Conversely, branches and other offices of Japanese corporations located outside Japan are regarded as exchange non-residents.

Foreign investors are defined in the Foreign Exchange Regulations as:

(i) individuals who do not reside in Japan;

(ii) corporations or other entities organized under the laws of foreign countries or whose principal offices are located outside Japan (excluding partnerships falling within (iv));

(iii) corporations of which 50% or more of the total voting rights are held, directly or indirectly, by individuals and/or corporations falling within (i) and/or (ii) above;

(iv) general partnerships or limited partnerships under Japanese law or any similar partnerships under the laws of foreign countries, where either: (A) 50% or more of the capital contributions to those entities are made by individuals who do not reside in Japan or certain other foreign investors or (B) a majority of the general partners of such entities are individuals who do not reside in Japan or certain other foreign investors; or

(v) corporations or other entities of which a majority of either (A) directors or other persons equivalent thereto or (B) directors or other persons equivalent thereto having the power of representation are individuals who do not reside in Japan.

Acquisition of Shares

Acquisition by an exchange non-resident of shares of a Japanese corporation from an exchange resident requires post facto reporting by the exchange resident to the Minister of Finance of Japan through the Bank of Japan. No such reporting requirement is imposed, however, if:

(i) the aggregate purchase price of the relevant shares is 100 million JPY or less;

(ii) the acquisition is affected through any bank, financial instruments business operator or other entity prescribed by the Foreign Exchange Regulations acting as an agent or intermediary; or

(iii) the acquisition constitutes an "inward direct investment" described below.

Inward Direct Investment in Shares of Listed Corporations

Inward Direct Investment

If a foreign investor acquires shares or voting rights of a Japanese corporation that is listed on a Japanese stock exchange, such as the shares of our common stock and ADSs, or that is traded on an over-the-counter market in Japan and, as a result of the acquisition, the foreign investor, in combination with any existing holdings and holdings of its closely-related persons (as defined in the Foreign Exchange Regulations), directly or indirectly holds 1% or more of (i) the total issued shares or (ii) the total voting rights of the relevant corporation (shares and voting rights of the relevant corporation to be acquired are referred to as the "Inward Direct Investment Shares"), such an acquisition constitutes an "inward direct investment" under the FEFTA.

Prior Notification

Where a foreign investor intends to acquire the Inward Direct Investment Shares, and any of the business conducted by the investee Japanese corporation falls within any business sectors designated under the Foreign Exchange Regulations (the "Designated Business Sectors", *Shitei-Gyoshu*) (which is the case for Takeda), in principle, a notification of the acquisition must be made in advance to the Minister of Finance and any other competent Ministers having jurisdiction over that Japanese corporation (including the MHLW).

If such a notification is made, the proposed acquisition cannot be consummated until 30 days have passed from the date thereof (this period is referred to as the "Screening Period"); provided, however, that the Screening Period will be shortened unless any of the relevant Ministers finds it necessary to check whether the proposed acquisition should be restricted from the viewpoint of national security or certain other factors, and may be shortened to 5 business days, if the proposed acquisition is determined not to raise such concerns. If the relevant Ministers find it necessary to check whether the proposed acquisition should be restricted, the Ministers may extend the Screening Period for up to five months; and the Ministers may eventually recommend any modifications to, or abandonment of, the proposed acquisition if necessary from the viewpoint of national security or certain other factors. If the foreign investor does not accept any of the recommendations, the relevant Ministers may order that the proposed acquisition be modified or abandoned.

Foreign investors acquiring the Inward Direct Investment Shares by way of a stock split are not subject to these notification requirements.

In addition, in the event a foreign investor, in combination with any holdings of its closely-related persons, directly or indirectly holds 1% or more of the total voting rights of a Japanese listed corporation engaging in the Designated Business Sectors, certain other activities of such a foreign investor such as (i) voting for appointment of his/herself or a person related thereto (as defined in the Foreign Exchange Regulations) as a director or corporate auditor of such corporation and (ii) proposal and voting for transfer or abolishment of business activities related to the Designated Business Sectors of such a corporation also constitute "inward direct investments" and, as a result, are subject to the prior notification requirements under the FEFTA.

Exemption from Prior Notification

Irrespective of the foregoing, where any of the business conducted by the investee Japanese corporation falls within certain Designated Business Sectors specified in the Foreign Exchange Regulations (the "Core Sectors", Core Gyoshu) (we are currently conducting business falling within the Core Sectors), the foreign investor (including (a) the foreign financial institutions specified in the Foreign Exchange Regulations and (b) sovereign wealth funds or public pension funds which have been accredited by the Japanese government and excluding the foreign financial institutions specified in the Foreign Exchange Regulations), who (i) acquires less than 10% of the Inward Direct Investment Shares (comprised of the aggregate amount of any existing holdings and holdings of its closely-related persons) of such a Japanese corporation, and (ii) complies with the following conditions is not required to make a prior notification upon his/her acquisition of the Inward Direct Investment Shares since an exemption therefrom is applicable, as long as;

(a) the foreign investor and its related persons (as defined in the Foreign Exchange Regulations) will not become board members of such corporation or its certain related corporations;

(b) the foreign investor will not propose transfer or abolishment of the business activities related to the Designated Business Sectors to or at a general meeting of shareholders;

(c) the foreign investor will not access non-public information about the technology of such a corporation or its certain related corporations in relation to business activities related to Designated Business Sectors;

(d) the foreign investor will not attend the meetings of the board of directors or executive committees of corporation or its certain related corporations that make important decisions in connection with business activities related to the Core Sectors; and

(e) the foreign investor will not make any proposals, in a written form, to the board of directors or executive committees that make important decisions or their members of such corporation or its certain related corporations requesting that they respond and/or take any action in connection with business activities related to the Core Sectors by a certain deadline.

Further, foreign financial institutions specified in the Foreign Exchange Regulations who comply with conditions (a), (b) and (c) above are exempted from prior notification requirements.

This exemption is not applicable to certain types of foreign investors (for example, a foreign investor with a certain record of sanctions due to violation of the Foreign Exchange Regulations, or state-owned enterprises except those who are accredited by the Minister of Finance), and such foreign investors must file the prior notification set forth above.

Post Transaction Report

A foreign investor who has made a prior notification, as mentioned above must file a post transaction report (the "Post Transaction Report") with the Minister of Finance and any other competent Ministers having jurisdiction over that Japanese corporation within 45 days after his/hers acquisition of the Inward Direct Investment Shares.

A foreign investor who has acquired the Inward Direct Investment Shares in reliance on an exemption from prior notification, must, in principle, file a Post Transaction Report within 45 days after such acquisition, if the ratio of the total number of shares or voting rights held directly or indirectly by the foreign investor in combination with any existing holdings and holdings of its closely related persons after the acquisition to the number of (i) the total issued shares or (ii) the total voting rights of the relevant corporation reaches:

(i) 1% or more but less than 3% for the first time;

(ii) 3% or more but less than 10% for the first time; and

(iii) 10% or more for each acquisition.

Provided, however, that foreign financial institutions specified in the Foreign Exchange Regulations are only required to file a Post Transaction Report for (iii) above.

Foreign investors acquiring the Inward Direct Investment Shares by way of a stock split are not subject to the Post Transaction Report requirements.

Dividends and Proceeds of Sale

Under the Foreign Exchange Regulations, dividends paid on, and the proceeds from sales in Japan of, shares held by exchange non-residents may generally be converted into any foreign currency and repatriated abroad.

Reporting of Substantial Shareholdings

The Financial Instruments and Exchange Act of Japan and its related regulations require any person, regardless of residence, who has become beneficially, solely or jointly, a holder of more than 5% of the total issued shares of common stock of a corporation that is listed on a Japanese stock exchange, or that is traded on an over-the-counter market in Japan, to file with the Director of the relevant Local Finance Bureau of the Ministry of Finance, within five business days, a report concerning such shareholdings. With certain exceptions, a similar report must also be filed in respect of any subsequent change of 1% or more in any such holdings or any change in material matters set out in reports previously filed. For this purpose, shares issuable to such a person upon the exchange of exchangeable securities, conversion of convertible securities or exercise of warrants or stock acquisition rights (including those incorporated in bonds with stock acquisition rights) are taken into account in determining both the number of shares held by the holder and the total issued shares.

E. Taxation

Material U.S. Federal Income Tax Consequences

This section describes the material U.S. federal income tax consequences of owning ADSs. It applies to you only if you are a U.S. holder (as defined below) and you hold your ADSs as capital assets for tax purposes. This discussion addresses only U.S. federal income taxation and does not discuss all of the tax consequences that may be relevant to you in light of your individual circumstances, including foreign, state or local tax consequences, estate and gift tax consequences, and tax consequences arising under the Medicare contribution tax on net investment income or the alternative minimum tax. This section does not apply to you if you are a member of a special class of holders subject to special rules, including:

- a dealer in securities,
- a trader in securities that elects to use a mark-to-market method of accounting for securities holdings,
- a tax-exempt organization,
- a life insurance company,
- a person that actually or constructively owns 10% or more of the combined voting power of our voting stock or of the total value of our stock,
- a person that holds ADSs as part of a straddle or a hedging or conversion transaction,
- a person that purchases or sells ADSs as part of a wash sale for tax purposes, or
- a person whose functional currency is not the U.S. dollar.

This section is based on the Internal Revenue Code of 1986, as amended, its legislative history, existing and proposed regulations, published rulings and court decisions, all as currently in effect, as well as on the Convention Between the Government of the United States of America and the Government of Japan for the Avoidance of Double Taxation and the Prevention of Fiscal Evasion with Respect to Taxes on Income (the “Treaty”). These laws are subject to change, possibly on a retroactive basis. In addition, this section is based in part upon the assumption that each obligation in the deposit agreement will be performed in accordance with its terms.

If an entity or arrangement that is treated as a partnership for U.S. federal income tax purposes holds the ADSs, the U.S. federal income tax treatment of a partner will generally depend on the status of the partner and the tax treatment of the partnership. A partner in a partnership holding the ADSs should consult its tax advisor with regard to the U.S. federal income tax treatment of an investment in the ADSs.

You are a U.S. holder if you are a beneficial owner of ADSs and you are for U.S. federal income tax purposes:

- a citizen or resident of the U.S.,
- a domestic corporation,
- an estate whose income is subject to U.S. federal income tax regardless of its source, or

- a trust if a U.S. court can exercise primary supervision over the trust's administration and one or more U.S. persons are authorized to control all substantial decisions of the trust.

You should consult your own tax advisor regarding the U.S. federal, state and local tax consequences of owning and disposing of ADSs in your particular circumstances.

In general, and taking into account the earlier assumptions, for U.S. federal income tax purposes, if you hold ADRs evidencing ADSs, you will be treated as the owner of the shares represented by those ADRs. Exchanges of shares for ADRs, and ADRs for shares, generally will not be subject to U.S. federal income tax.

The tax treatment of your ADSs will depend in part on whether or not we are classified as a passive foreign investment company, or PFIC, for U.S. federal income tax purposes. Except as discussed below under "PFIC Rules", this discussion assumes that we are not classified as a PFIC for U.S. federal income tax purposes.

Distributions

Under U.S. federal income tax laws, if you are a U.S. holder, the gross amount of any distribution we pay out of our current or accumulated earnings and profits (as determined for U.S. federal income tax purposes), other than certain pro-rata distributions of our shares, will be treated as a dividend that is subject to U.S. federal income taxation. If you are a non-corporate U.S. holder, dividends that constitute qualified dividend income will be taxable to you at the preferential rates applicable to long-term capital gains provided that you hold the ADSs for more than 60 days during the 121-day period beginning 60 days before the ex-dividend date and meet other holding period requirements. Dividends that we distribute with respect to the ADSs will be qualified dividend income if the ADSs are readily tradable on an established securities market in the U.S. in the year that we distribute the dividend. Our ADSs are listed on the NYSE which is considered an established securities market in the U.S. We therefore expect that dividends that we distribute on our ADSs will be qualified dividend income, provided that you satisfy the aforementioned holding period requirements.

You must include any Japanese tax withheld from the dividend payment in this gross amount even though you do not in fact receive it. The dividend is taxable to you when the depositary receives the dividend, actually or constructively. The dividend will not be eligible for the dividends-received deduction generally allowed to U.S. corporations in respect of dividends received from other U.S. corporations. The amount of the dividend distribution that you must include in income will be the U.S. dollar value of the yen payments made, determined at the spot yen/U.S. dollar rate on the date the dividend is distributed, even if the depositary (a) converts the yen into U.S. dollars at a different rate or (b) does not convert the dividend payment into U.S. dollars. If the depositary converts the yen into U.S. dollars at a different rate, then you will recognize U.S. source ordinary income (that would not be treated as qualified dividends) or loss equal to the difference between the U.S. dollars that you receive and the U.S. dollar amount that you included as dividend income. If the depositary does not convert the dividend payment into U.S. dollars, then you will recognize U.S. source ordinary income (that would not be treated as qualified dividend income) or loss upon a conversion of the yen into U.S. dollars equal to the difference between the U.S. dollars that you receive in the conversion and the U.S. dollar amount that you included as dividend income.

Distributions in excess of current and accumulated earnings and profits, as determined for U.S. federal income tax purposes, will be treated as a non-taxable return of capital to the extent of your basis in the ADSs and thereafter as capital gain. However, we do not expect to calculate earnings and profits in accordance with U.S. federal income tax principles. Accordingly, you should expect to generally treat distributions we make as dividends.

Subject to certain limitations, the Japanese tax withheld in accordance with the Treaty and paid over to Japan will be creditable or deductible against your U.S. federal income tax liability. However, under recently issued United States Treasury regulations, it is possible that such withholding tax will not be creditable unless the U.S. holder is eligible to claim the benefits of the Treaty and elects to apply the Treaty. Special rules apply in determining the foreign tax credit limitation with respect to dividends that are subject to the preferential tax rates. To the extent a reduction or refund of the tax withheld is available to you under Japanese law or under the Treaty, the amount of tax withheld that could have been reduced or that is refundable will not be eligible for credit against your U.S. federal income tax liability.

Dividends will generally be income from sources outside the U.S. and will generally be "passive" income for purposes of computing the foreign tax credit allowable to you. However, if (a) we are 50% or more owned, by vote or value, by U.S. persons and (b) at least 10% of our earnings and profits are attributable to sources within the U.S., then for foreign tax credit purposes, a portion of our dividends would be treated as derived from sources within the U.S. With respect to any dividend paid for any taxable year, the U.S. source ratio of our dividends for foreign tax credit purposes would be equal to the portion of our earnings and profits from sources within the U.S. for such taxable year, divided by the total amount of our earnings and profits for such taxable year.

Distributions of additional shares to you with respect to ADSs that are made as part of a pro rata distribution to all of our shareholders generally will not be subject to U.S. federal income tax.

Capital Gains

If you are a U.S. holder and you sell or otherwise dispose of your ADSs, you will recognize a capital gain or loss for U.S. federal income tax purposes equal to the difference between the U.S. dollar value of the amount that you realize and your tax basis, determined in U.S. dollars, in your ADSs. Capital gain of a non-corporate U.S. holder is generally taxed at preferential rates where the property is held for more than one year. The gain or loss will generally be income or loss from sources within the U.S. for foreign tax credit limitation purposes.

PFIC Rules

We believe that ADSs should not currently be treated as stock of a PFIC for U.S. federal income tax purposes and we do not expect to become a PFIC in the foreseeable future. However, this conclusion is a factual determination that is made annually and thus may be subject to change. It is therefore possible that we could become a PFIC in a future taxable year.

In general, if you are a U.S. holder, we will be a PFIC with respect to you if for any taxable year in which you held our ADSs:

- at least 75% of our gross income for the taxable year is passive income or
- at least 50% of the value, determined on the basis of a quarterly average, of our assets is attributable to assets that produce or are held for the production of passive income.

"Passive income" generally includes dividends, interest, gains from the sale or exchange of investment property, rents and royalties (other than certain rents and royalties derived in the active conduct of a trade or business) and certain other specified categories of income. If a foreign corporation owns at least 25% by value of the stock of another corporation, the foreign corporation is treated for purposes of the PFIC tests as owning its proportionate share of the assets of the other corporation, and as receiving directly its proportionate share of the other corporation's income.

If we are treated as a PFIC, and you are a U.S. holder that did not make a mark-to-market election, as described below, you will generally be subject to special rules with respect to:

- any gain you realize on the sale or other disposition of your ADSs and
- any excess distribution that we make to you (generally, any distributions to you during a single taxable year, other than the taxable year in which your holding period in the ADSs begins, that are greater than 125% of the average annual distributions received by you in respect of the ADSs during the three preceding taxable years or, if shorter, your holding period for the ADSs that preceded the taxable year in which you receive the distribution).

Under these rules:

- the gain or excess distribution will be allocated ratably over your holding period for the ADSs,
- the amount allocated to the taxable year in which you realized the gain or excess distribution or to prior years before the first year in which we were a PFIC with respect to you will be taxed as ordinary income,
- the amount allocated to each other prior year will be taxed at the highest tax rate in effect for that year, and
- the interest charge generally applicable to underpayments of tax will be imposed in respect of the tax attributable to each such year.

Special rules apply for calculating the amount of the foreign tax credit with respect to excess distributions by a PFIC.

If we are a PFIC in a taxable year and our ADSs are treated as "marketable stock" in such year, you may make a mark-to-market election with respect to your ADSs. If you make this election, you will not be subject to the PFIC rules described above. Instead, in general, you will include as ordinary income each year the excess, if any, of the fair market value of your ADSs at the end of the taxable year over your adjusted basis in your ADSs. You will also be allowed to take an ordinary loss in respect of the excess, if any, of the adjusted basis of your ADSs over their fair market value at the end of the taxable year (but only to the extent of the net amount of previously included income as a result of the mark-to-market election). Your basis in the ADSs will be adjusted to reflect any such income or loss amounts. Any gain that you recognize on the sale or other disposition of your ADSs would be ordinary income and any loss would be an ordinary loss to the extent of the net amount of previously included income as a result of the mark-to-market election and, thereafter, a capital loss.

Your ADSs will generally be treated as stock in a PFIC if we were a PFIC at any time during your holding period in your ADSs, even if we are not currently a PFIC.

In addition, notwithstanding any election you make with regard to the ADSs, dividends that you receive from us will not constitute qualified dividend income to you if we are a PFIC (or are treated as a PFIC with respect to you) either in the taxable year of the distribution or the preceding taxable year. Dividends that you receive that do not constitute qualified dividend income are not eligible for taxation at the preferential rates applicable to qualified dividend income. Instead, you must include the gross amount of any such dividend paid by us out of our accumulated earnings and profits (as determined for U.S. federal income tax purposes) in your gross income, and it will be subject to tax at rates applicable to ordinary income.

If you own ADSs during any year that we are a PFIC with respect to you, you may be required to file Internal Revenue Service Form 8621. However, as mentioned above, we believe that ADSs should not currently be treated as stock of a PFIC for U.S. federal income tax purposes and we do not expect to become a PFIC in the foreseeable future.

Japanese Taxation

The following is a general summary of the principal Japanese tax consequences (limited to national tax) to owners of shares of our common stock, in the form of shares or ADSs, who are non-resident individuals of Japan or who are non-Japanese corporations without a permanent establishment in Japan, collectively referred to in this section as non-resident holders. The statements below regarding Japanese tax laws are based on the laws and treaties in force and as interpreted by the Japanese tax authorities as of the date of this annual report, and are subject to changes in applicable Japanese laws, tax treaties, conventions or agreements, or in the interpretation of them, occurring after that date. This summary is not exhaustive of all possible tax considerations that may apply to a particular investor, and potential investors are advised to satisfy themselves as to the overall tax consequences of the acquisition, ownership and disposition of shares of our common stock, including, specifically, the tax consequences under Japanese law, under the laws of the jurisdiction of which they are resident and under any tax treaty, convention or agreement between Japan and their country of residence, by consulting their own tax advisors.

For the purpose of Japanese tax law and the tax treaty between the U.S. and Japan, a U.S. holder of ADSs will generally be treated as the owner of the shares underlying the ADSs evidenced by the ADRs.

Generally, a non-resident holder of shares or ADSs will be subject to Japanese income tax collected by way of withholding on dividends (meaning in this section distributions made from our retained earnings for the Companies Act purposes) we pay with respect to shares of our common stock and such tax will be withheld prior to payment of dividends. Stock splits generally are not subject to Japanese income or corporation taxes.

In the absence of any applicable tax treaty, convention or agreement reducing the maximum rate of Japanese withholding tax or allowing exemption from Japanese withholding tax, the rate of the Japanese withholding tax applicable to dividends paid by Japanese corporations on their shares of stock to non-resident holders is generally 20.42% (or 20% for dividends due and payable on or after January 1, 2038) under Japanese tax law. However, with respect to dividends paid on listed shares issued by a Japanese corporation (such as shares or ADSs) to non-resident holders, other than any individual shareholder who holds 3% or more of the total number of shares issued by the relevant Japanese corporation (to whom the aforementioned withholding tax rate will still apply), the aforementioned withholding tax rate is reduced to (i) 15.315% for dividends due and payable up to and including December 31, 2037 and (ii) 15% for dividends due and payable on or after January 1, 2038. The withholding tax rates described above include the special reconstruction surtax (2.1% multiplied by the original applicable withholding tax rate, i.e., 15% or 20%, as the case may be), which is imposed during the period from and including January 1, 2013 to and including December 31, 2037, to fund the reconstruction from the Great East Japan Earthquake.

If distributions were made from our capital surplus, rather than retained earnings, for the Companies Act purposes, the portion of such distributions in excess of the amount corresponding to a pro rata portion of return of capital as determined under Japanese tax laws would be deemed dividends for Japanese tax purposes, while the rest would be treated as return of capital for Japanese tax purposes. The deemed dividend portion, if any, would generally be subject to the same tax treatment as dividends as described above, and the return of capital portion would generally be treated as proceeds derived from the sale of shares and subject to the same tax treatment as sale of shares of our common stock as described below. Distributions made in consideration of repurchase by us of our own shares or in connection with certain reorganization transactions will be treated substantially in the same manner.

Japan has income tax treaties whereby the withholding tax rate (including the special reconstruction surtax) may be reduced, generally to 15%, for portfolio investors, with, among others, Canada, Denmark, Finland, Germany, Ireland, Italy, Luxembourg, New Zealand, Norway and Singapore, while the income tax treaties with, among others, Australia, Belgium, France, Hong Kong, the Netherlands, Portugal, Sweden, Switzerland, the United Arab Emirates, the U.K. and the U.S. generally reduce the withholding tax rate to 10% for portfolio investors and the income tax treaty, among others, with Spain generally reduce the withholding tax rate to 5% for portfolio investors. In addition, under the income tax treaty between Japan and the U.S., dividends paid to pension funds which are qualified U.S. residents eligible to enjoy treaty benefits are exempt from Japanese income taxation by way of withholding or otherwise unless the dividends are derived from the carrying on of a business, directly or indirectly, by the pension funds. Similar treatment is applicable to dividends paid to pension funds under the income tax treaties between Japan and, among others, Belgium, Denmark, the Netherlands, Spain, Switzerland, and the U.K. Under Japanese tax law, any reduced maximum rate applicable under a tax treaty shall be available when such maximum rate is below the rate otherwise applicable under the Japanese tax law referred to in the second preceding paragraph with respect to the dividends to be paid by us on our shares or ADSs.

Non-resident holders of our shares who are entitled under an applicable tax treaty to a reduced rate of, or exemption from, Japanese withholding tax on any dividends on our shares, in general, are required to submit, through the withholding agent to the relevant tax authority prior to the payment of dividends, an Application Form for Income Tax Convention regarding Relief from Japanese Income Tax and Special Income Tax for Reconstruction on Dividends together with any required forms and documents. A standing proxy for a non-resident holder of shares of our common stock or ADSs may be used in order to submit the application on a non-resident holder's behalf. In this regard, a certain simplified special filing procedure is available for non-resident holders to claim treaty benefits of reduction of or exemption from Japanese withholding tax, by submitting a Special Application Form for Income Tax Convention regarding Relief from Japanese Income Tax and Special Income Tax for Reconstruction on Dividends of Listed Stock, together with any required forms or documents. If the depositary needs investigation to identify whether any non-resident holders of ADSs are entitled to claim treaty benefits of exemption from or reduction of Japanese withholding tax, the depositary or its agent submits an application form before payment of dividends so that the withholding cannot be made in connection with such holders for eight months after the

record date concerning such payment of dividends. If it is proved that such holders are entitled to claim treaty benefits of exemption from or reduction of Japanese withholding tax within the foregoing eight-month period, the depositary or its agent submits another application form together with certain other documents so that such holder can be subject to exemption from or reduction of Japanese withholding tax. To claim this reduced rate or exemption, such a non-resident holder of ADSs will be required to file a proof of taxpayer status, residence and beneficial ownership, as applicable, and to provide other information or documents as may be required by the depositary. Non-resident holders who are entitled, under any applicable tax treaty, to a reduced rate of Japanese withholding tax below the rate otherwise applicable under Japanese tax law, or exemption therefrom, as the case may be, but fail to submit the required application in advance may nevertheless be entitled to claim a refund from the relevant Japanese tax authority of withholding taxes withheld in excess of the rate under an applicable tax treaty (if such non-resident holders are entitled to a reduced treaty rate under the applicable tax treaty) or the full amount of tax withheld (if such non-resident holders are entitled to an exemption under the applicable tax treaty), as the case may be, by complying with a certain subsequent filing procedure. We do not assume any responsibility to ensure withholding at the reduced treaty rate, or exemption therefrom, for shareholders who would be eligible under an applicable tax treaty but who do not follow the required procedures as stated above.

Gains derived from the sale of our shares or ADSs outside Japan by a non-resident holder that is a portfolio investor will generally not be subject to Japanese income or corporation taxes. Japanese inheritance and gift taxes, at progressive rates, may be payable by an individual who has acquired from another individual our shares or ADSs as a legatee, heir or done, even if none of the acquiring individual, the decedent or the donor is a Japanese resident.

F. Dividends and Paying Agents

Not applicable.

G. Statement by Experts

Not applicable.

H. Documents on Display

We have filed this annual report with the SEC under the Exchange Act with respect to the ADSs. We are subject to the information requirements of the Exchange Act and, in accordance therewith, we are required to file annual reports on Form 20-F and furnish other reports and information on Form 6-K with the SEC.

A copy of our filings may be reviewed without charge at the SEC's web site at www.sec.gov that contains reports and other information regarding registrants that file electronically with the SEC. Such filings can be also viewed on our web site at https://www.takeda.com/investors/reports/sec-filings/. As a foreign private issuer, we are exempt from the rules under the Exchange Act prescribing the furnishing and content of proxy statements to shareholders.

I. Subsidiary Information

Not applicable.

J. Annual Report to Security Holders

We intend to submit any annual report to security holders required to be furnished on Form 6-K in electronic format in accordance with the EDGAR Filer Manual.

Item 11. Quantitative and Qualitative Disclosures about Market Risk

We are exposed to market risks primarily from changes in foreign currency exchange rates, interest rate changes and changes in the value of our investment securities. The information required under this Item 11 is set forth in Note 27 to our audited consolidated financial statements included in this annual report.

Item 12. Description of Securities Other Than Equity Securities

A. Debt Securities

Not applicable.

B. Warrants and Rights

Not applicable.

C. Other Securities

Not applicable.

D. American Depositary Shares

Each ADS represents one-half of one share of our common stock deposited with our depositary's (The Bank of New York Mellon) custodian (Sumitomo Mitsui Banking Corporation) in Japan. Each ADS will also represent any other securities, cash or other property which may be held by the depositary from time to time. The deposited shares of our common stock, together with any other securities, cash or other property held by the depositary are referred to as the "deposited securities."

Fees and Expenses

Persons depositing or withdrawing shares of our common stock or ADS holders must pay:	*For:*
5.00 USD (or less) per 100 ADSs (or portion of 100 ADSs)	Issue of ADSs, including issues resulting from a distribution of shares of our common stock or rights or other property Cancellation of ADSs for the purpose of withdrawal, including if the deposit agreement terminates
0.05 USD (or less) per ADS	Any cash distribution to ADS holders
A fee equivalent to the fee that would be payable if securities distributed to ADS holders had been shares of our common stock and the shares of our common stock had been deposited for issuance of ADSs	Distribution of securities distributed to holders of deposited securities (including rights) that are distributed by the depositary to ADS holders
0.05 USD (or less) per ADS per calendar year	Depositary services
Registration or transfer fees	Transfer and registration of shares of our common stock on our share register to or from the name of the depositary or its agent when persons deposit or withdraw shares of our common stock
Expenses of the depositary	Cable and facsimile transmissions (when expressly provided in the deposit agreement) Converting foreign currency to U.S. dollars
Taxes and other governmental charges the depositary or the custodian have to pay on any ADSs or shares of our common stock underlying ADSs, such as stock transfer taxes, stamp duty or withholding taxes	As necessary
Any charges incurred by the depositary or its agents for servicing the deposited securities	As necessary

The depositary collects its fees for delivery and surrender of ADSs directly from investors depositing shares of our common stock or surrendering ADSs for the purpose of withdrawal or from intermediaries acting for them. The depositary collects fees for making distributions to investors by deducting those fees from the amounts distributed or by selling a portion of distributable property to pay the fees. The depositary may collect its annual fee for depositary services by deduction from cash distributions or by directly billing investors or by charging the book-entry system accounts of participants acting for them. The depositary may collect any of its fees by deduction from any cash distribution payable (or by selling a portion of securities or other property distributable) to ADS holders that are obligated to pay those fees. The depositary may generally refuse to provide fee-attracting services until its fees for those services are paid.

In performing its duties under the deposit agreement, the depositary may use brokers, dealers, foreign currency dealers or other service providers that are owned by or affiliated with the depositary and that may earn or share fees, spreads or commissions.

The depositary may convert currency itself or through any of its affiliates and, in those cases, acts as principal for its own account and not as agent, advisor, broker or fiduciary on behalf of any other person and earns revenue, including, without limitation, transaction spreads, that it will retain for its own account. The revenue is based on, among other things, the difference between the exchange rate assigned to the currency conversion made under the deposit agreement and the rate that the depositary or its affiliate receives when buying or selling foreign currency for its own account. The depositary makes no representation that the exchange rate used or obtained in any currency conversion under the deposit agreement will be the most favorable rate that could be obtained at the time or that the method by which that rate will be determined will be the most favorable to ADS holders, subject to the depositary's obligations under the deposit agreement. The methodology used to determine exchange rates used in currency conversions is available upon request.

Payment of Taxes

ADS holders will be responsible for any taxes or other governmental charges payable on their ADSs or on the deposited securities represented by any of their ADSs. The depositary may refuse to register any transfer of ADSs or allow an ADS holder to withdraw the deposited securities represented by his or her ADSs until those taxes or other charges are paid. It may apply payments owed to such ADS holder or sell deposited securities represented by such ADS holder's ADSs to pay any taxes owed and such ADS holder will remain liable for any deficiency. If the depositary sells deposited securities, it will, if appropriate, reduce the number of ADSs to reflect the sale and pay to ADS holders any proceeds, or send to ADS holders any property, remaining after it has paid the taxes.

Direct and Indirect Payments by the Depositary

The depositary has agreed to make revenue sharing payments to us based on a fixed portion of the net issuance, net cancellation and net depositary servicing fees received by it under the deposit agreement, subject to a minimum annual payment based on the total of such fees received by the depositary. In the fiscal year ended March 31, 2023, we received 1.0 million USD of such revenue sharing payments.

The depositary has also agreed to waive fees and expenses for services provided to us, to ADS holders or to their respective brokers by the depositary in connection with the establishment, administration and ongoing servicing of the ADS program. Furthermore, the depositary has agreed to waive fees for certain value-added services, including training for our staff, investor relations advisory services and access to the depositary's analytics and reporting platform. Accordingly, in the fiscal year ended March 31, 2023, the depositary waived approximately 0.1 million USD of fees and expenses.

Part II

Item 13. Defaults, Dividend Arrearages and Delinquencies

Not applicable.

Item 14. Material Modifications to the Rights of Security Holders and Use of Proceeds

Not applicable.

Item 15. Controls and Procedures

Disclosure Controls and Procedures

We have carried out an evaluation under the supervision and with the participation of our management, including our CEO and CFO, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, as of March 31, 2023. Disclosure controls and procedures require that information to be disclosed in the reports we file or submit under the Exchange Act is recorded, processed, summarized and reported as and when required, within the time periods specified in the applicable rules and forms, and that such information is accumulated and communicated to our management, including our CEO and CFO, as appropriate to allow timely decisions regarding required disclosure. There are inherent limitations to the effectiveness of any system of disclosure controls and procedures, including the possibility of human error and the circumvention or overriding of the controls and procedures. Accordingly, even effective disclosure controls and procedures can only provide reasonable assurance of achieving their control objectives. Based upon our evaluation, our CEO and CFO have concluded that, as of March 31, 2023, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Annual Report on Internal Control Over Financial Reporting

Management is responsible for establishing and maintaining adequate internal control over financial reporting, as defined in Rule 13a-15(f) and 15d-15(f) under the Exchange Act. Takeda's internal control over financial reporting is designed to provide reasonable assurance to management regarding the reliability of financial reporting and the preparation and fair presentation of its consolidated financial statements in accordance with IFRS. Management assessed the effectiveness of Takeda's internal control over financial reporting as of March 31, 2023 based on the framework in Internal Control - Integrated Framework (2013 framework) issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on the assessment, management concluded that, Takeda's internal control over financial reporting is effective as of March 31, 2023. The effectiveness of internal control over financial reporting as of March 31, 2023 has been audited by KPMG AZSA LLC, our independent registered public accounting firm. Its audit report on the effectiveness of Takeda's internal control over financial reporting is included in the audited consolidated financial statements.

Attestation Report of the Registered Public Accounting Firm

See "—Report of Independent Registered Public Accounting Firm" included in the audited consolidated financial statements.

Changes in Internal Control Over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) that occurred during the fiscal year ended March 31, 2023 that have materially affected, or were reasonably likely to materially affect, our internal control over financial reporting.

Item 16A. Audit Committee Financial Expert

Our board of directors has determined that Mr. Koji Hatsukawa, an external director and member of our Audit and Supervisory Committee, is an "audit committee financial expert" as defined in Item 16A of Form 20-F and is "independent" as defined in the listing standards of the New York Stock Exchange as applicable to Takeda and as further set forth in Rule 10A-3 under the Exchange Act.

Item 16B. Code of Ethics

We have adopted the Takeda Global Code of Conduct, which applies to all of our employees, including our principal executive officer, principal financial officer, principal accounting officer and persons performing similar functions. The Takeda Global Code of Conduct is posted on our corporate website at https://www.takeda.com/who-we-are/global-ethics-compliance/. No waivers to the Global Code of Conduct were granted to our principal executive officer, principal financial officer, principal accounting officer and persons performing similar functions in the fiscal year ended March 31, 2023.

Item 16C. Principal Accountant Fees and Services

Audit and Non-Audit Fees

The following table sets forth the fees billed to us by our independent certified public accountant, KPMG AZSA LLC (including its Japanese and non-Japanese affiliates), in the fiscal years ended March 31, 2022 and 2023:

	For the fiscal year ended March 31,	
	2022	2023
	(billions of yen)	
Audit fees [(1)]	¥ 3.58	¥ 3.64
Audit related fees [(2)]	0.04	0.05
Tax fees [(3)]	0.00	—
Other fees [(4)]	0.00	0.02
Total fees	¥ 3.62	¥ 3.71

Notes:
(1) Audit fees were related to the audit of our consolidated financial statements and other services provided in connection with statutory and regulatory filings or engagements.
(2) Audit related fees include fees related to services for consent letter regarding the issuance of Form S-8 and services for comfort letters regarding the issuance of bonds.
(3) Tax fees were related to tax compliance and other tax-related services.
(4) Other fees in the fiscal years ended March 31, 2023 include services related to non-financial information.

Pre-Approval Policies and Procedures

Pursuant to Rule 2-01(c)(7)(i) of Regulation S-X, we have adopted policies and procedures under which all services (including permissible non-audit services) for which we or our subsidiaries engage our independent certified public accountant, KPMG AZSA LLC, and its affiliates must be approved by our Audit and Supervisory Committee prior to entering into an engagement.

All audit services are subject to the pre-approval by the Audit and Supervisory Committee in principle, regardless of monetary value. Audit services include statutory or financial statement audits for us and our subsidiaries, services associated with the audit of our management's report on internal controls over financial reporting and services associated with the review of our quarterly financial statements. On a yearly basis, our management, following a review by our Chief Financial Officer, presents the proposed audit services to our Audit and Supervisory Committee for approval, and proposes audit fees on an entity basis to the Audit and Supervisory Committee for its consent. Once such services and fees are approved or consented to, as applicable, any additional audit services must be separately presented to and approved by our Audit and Supervisory Committee.

Permissible non-audit services, which are limited to certain services permissible under applicable regulation and our internal rules, are pre-approved by the Audit and Supervisory Committee for individual services below 25 million JPY annually, subject to an aggregate annual limit of up to 250 million JPY for all such services. These services are subject to review by our management for compliance with our internal policies. All non-audit services exceeding the applicable monetary limits or which are not clearly within the scope of permitted non-audit services must be presented to and pre-approved by the Audit and Supervisory Committee. All services relating to tax or internal control are also subject to separate presentation to and pre-approval by the Audit and Supervisory Committee regardless of monetary value.

Item 16D. Exemptions from the Listing Standards for Audit Committees

As of the date of this annual report, we do not rely on any of the exemptions contained in paragraph (b)(1)(iv), the general exemption contained in paragraph (c)(3) or the last sentence of paragraph (a)(3) of Rule 10A-3 under the Exchange Act.

Item 16E. Purchases of Equity Securities by the Issuer and Affiliated Purchasers

The following table sets forth purchases of our common stock by us and our affiliated purchasers during the fiscal year ended March 31, 2023:

	Total number of shares purchased [1]	Average price paid per share (yen)	Total number of shares purchased as part of publicly announced plans or programs [2]	Maximum approximate value of shares that may yet be purchased under the plans or programs (billions of yen)
April 1 to April 30, 2022	6,907,879	¥ 3,618.24	6,907,500	¥ —
May 1 to May 31, 2022	554,846	3,692.56	554,400	—
June 1 to June 30, 2022	396	3,631.36	—	—
July 1 to July 31, 2022	490	3,921.73	—	—
August 1 to August 31, 2022	742	3,821.76	—	—
September 1 to September 30, 2022	504	3,851.94	—	—
October 1 to October 31, 2022	522	3,753.79	—	—
November 1 to November 30, 2022	318	3,865.88	—	—
December 1 to December 31, 2022	445	4,062.51	—	—
January 1 to January 31, 2023	241	4,081.51	—	—
February 1 to February 28, 2023	431	4,167.35	—	—
March 1 to March 31, 2023	239	4,290.56	—	—
Total	7,467,053	¥ 3,896.60	7,461,900	¥ —

Notes:

(1) Total number of shares purchased in the above table reflect (a) purchases of shares in relation to stock-based incentive compensation plans, (b) acquisition of own shares in relation to up to the 100.0 billion JPY share buyback approved by our board of directors on October 28, 2021 and (c) purchases of shares constituting less than one "unit" (100 shares).
A total of 5,153 shares were purchased other than through publicly announced plans or programs during the fiscal year ended March 31, 2023, due to our purchase of shares constituting less than one "unit" (100 shares) from holders of shares constituting less than one unit at the current market price of those shares.

(2) Total number of shares purchased as part of publicly announced plans or programs in the above table reflect (a) purchases of shares in May 2022 in relation to stock-based incentive compensation plans and (b) acquisition of own shares during April 2022 in relation to the share buyback resolved at the board of directors meeting on October 28, 2021.
On May 11, 2022, we announced that our board of directors resolved to continue the stock compensation plan which was introduced as a long-term incentive plan for members of the board of directors in the fiscal year ended March 31, 2017, as well as to continue the stock grant system which was introduced in the fiscal year ended March 31, 2015 as a global long-term incentive plan for Company Group Management in Japan.
On October 28, 2021, we announced that our board of directors had resolved to approve the repurchase of shares of common stock by us, consisting of a total of up to 35 million shares for a total aggregate purchase price of up to 100.0 billion JPY to be purchased through a trust bank between November 2, 2021 and April 29, 2022. Pursuant to this plan, we repurchased an aggregate of 6,907,500 shares during April 2022.

Item 16F. Change in Registrant's Certifying Accountant

Not applicable.

Item 16G. Corporate Governance

Our ADSs have been listed on the NYSE since 2018. NYSE-listed companies are required to comply with corporate governance standards under Section 303A of the NYSE Listed Company Manual. However, as a foreign private issuer, we are permitted to follow home country practices in lieu of certain provisions of Section 303A. Below, we provide a brief description of significant differences between the NYSE listing standards applicable to U.S. domestic issuers and our corporate governance policies pursuant to 303A.11 of the NYSE Listed Company Manual.

Composition of the Board (303A.01)

Under the NYSE listing standards, U.S. domestic issuers are required to have a majority of directors meeting the independence tests set forth in the NYSE listed company manual.

Takeda is a "company with audit and supervisory committee" as defined in the Companies Act. Companies with audit and supervisory committees are not required to have a majority of independent directors. Such companies must have a board of directors as well as an audit and supervisory committee consisting of at least three of its directors. A majority of the members of the audit and supervisory committee must be "external directors" as defined under the Companies Act, which differs from, and may be considered to be less stringent than, the director independence standards under the NYSE listed company manual in that the former constitute prescriptive requirements relating to service as company management. Additionally, under the regulations of the Tokyo Stock Exchange, we are required to have at least one director who is "independent" for the purposes of such regulations, which are more stringent than the requirements for "external directors" under the Companies Act, but also constitute certain prescriptive requirements relating to the director's current or previous relationships with the company.

Our board of directors consists of 15 directors, of which 12 are external directors under the Companies Act. Our Audit and Supervisory Committee is comprised of four of our directors, all of whom qualify as external directors under this standard. Each of our external directors also qualifies as "independent" as described under "Director Independence (303A.02)" below, and each of the members of our Audit and Supervisory Committee qualifies as "independent" for purposes of Rule 10A-3 under the Exchange Act.

Directors who are Audit and Supervisory Committee members are elected separately from our other directors. The term of office for a director who is an Audit and Supervisory Committee member is two years, whereas the term of office for other directors is one year.

Director Independence (303A.02)

We deem a director as being an "independent director" when such director also meets independence requirements stipulated in the regulations of the Tokyo Stock Exchange, on which our common stock is listed, and independence requirements established internally. These requirements differ in certain respects from the requirements under the NYSE listed company manual. Our internal independence standards emphasize the satisfaction of certain skills- or experience-based criteria in addition to meeting applicable regulatory and statutory independence standards.

Executive Sessions (303A.03)

The NYSE listed company manual requires that non-management directors of U.S. domestic issuers meet in regularly scheduled executive sessions without management. Although not required under Japanese law or Tokyo Stock Exchange rule, our independent external directors hold regularly scheduled executive sessions without management.

Composition of Committees (303A.04, 05, 06 and 07)

The NYSE listed company manual requires that U.S. domestic issuers establish a nomination/corporate governance committee and a compensation committee, each of which much be composed entirely of independent directors. The NYSE listed company manual also requires that all listed companies, including a foreign private issuer (as defined in the Exchange Act) such as us, establish an audit committee satisfying the requirements of Rule 10A-3 under the Exchange Act. Audit committees of U.S. domestic issuers are also subject to certain additional requirements under Section 303A.07 of the NYSE listed company manual.

Although the Companies Act does not require companies with audit and supervisory committees to establish nomination committees or compensation committees, we have voluntarily established such committees in order to ensure transparency. Our Nomination Committee consists of five directors (all of which are independent external directors for the purposes of Japanese law and the rules of the Tokyo Stock Exchange) plus one director as an observer who is not an external director. Director candidates nominated by our Board of Directors based on the advice of our Nomination Committee must be approved at our general meeting of shareholders. Unlike the nomination/corporate governance committees of U.S. domestic issuers, our Nomination Committee is not also responsible for corporate governance policies.

Our Compensation Committee consists of four directors (all of which are independent external directors for the purposes of Japanese law and the rules of the Tokyo Stock Exchange). The maximum total amount of compensation for our directors must be approved at our general meeting of shareholders, provided that the maximum total amounts for directors who are Audit and Supervisory Committee members and for other directors must be separately approved. The individual amounts of compensation for our directors (other than Audit and Supervisory Committee members) is

determined in accordance with the compensation standards determined by our board of directors or a resolution of our board of directors. The Board of Directors delegates the decision on the amount of compensation for individual directors to the Compensation Committee. The individual amounts of compensation for our Audit and Supervisory Committee members are determined by discussion among the Audit and Supervisory Committee members.

Our Audit and Supervisory Committee consists of four directors (all of whom are independent external directors for the purposes of Japanese law and the rules of the Tokyo Stock Exchange), and all of whom currently satisfy the independence requirements of Rule 10A-3 under the Exchange Act. Our Audit and Supervisory Committee does not necessarily satisfy all of the additional audit committee requirements applicable to NYSE-listed U.S. domestic companies under Section 303A.07, nor is it required to under the standards applicable to foreign private issuers under Section 303A. U.S. domestic issuers listed on NYSE are also required to disclose the respective charters of their nomination/corporate governance committee, their compensation committee and their audit committee. Although Japanese law and the regulations of the Tokyo Stock Exchange do not require us to disclose these charters, we voluntarily publish our Nomination Committee Charter, Compensation Committee Charter and Audit and Supervisory Committee Charter on our website in order to increase the transparency of our corporate governance.

Equity Compensation Plans (303A.08)

U.S. domestic issuers listed on NYSE are required to obtain the approval of shareholders for equity compensation plans and any material changes thereto, subject to certain limited exceptions.

Under Japanese law and the regulations of the Tokyo Stock Exchange, the adoption of an equity compensation plan, including for directors, requires shareholder approval. Pursuant to the approval of our general meeting of shareholders, we grant certain stock-based compensation to the directors. Stock acquisition rights or shares of common stock may be granted by resolution of the board of directors, except that, if stock acquisition rights or shares of common stock are to be granted on particularly favorable conditions, a special resolution of the general meeting of shareholders is required. The passage of a special resolution of the general meeting of shareholders requires the approval of two-thirds or more of the voting rights represented at a quorate general meeting of shareholders.

Corporate Governance Guidelines (303A.09)

U.S. domestic issuers listed on the NYSE must adopt and disclose corporate governance guidelines as set forth in the NYSE listed company manual. Japanese law and the regulations of the Tokyo Stock Exchange require us to disclose our basic views on corporate governance. In accordance with these requirements, we publish our Corporate Governance Report annually, which is posted on our website and furnished to the SEC under cover of Form 6-K, although this may not necessarily cover all of the same items as contemplated by the NYSE listed company manual.

Code of Business Conduct and Ethics (303A.10)

U.S. domestic issuers listed on NYSE are required to adopt and disclose a code of business conduct and ethics for directors, officers and employees, and promptly disclose any waivers of the code for directors or executive officers. Although not required to do so under the NYSE listed company manual, we have established a global code of business conduct and ethics, known as the Takeda Global Code of Conduct, which is posted on our website. Although the Takeda Global Code of Conduct functions as a code of business conduct and ethics, it is not required to cover all of the same areas as that of a U.S. domestic issuer under the NYSE listed company manual. Pursuant to the requirements of Form 20-F, waivers, if any, to the Takeda Global Code of Conduct given to our directors or senior management are disclosed by us in our annual reports on Form 20-F. No such waivers were granted in the fiscal year ended March 31, 2023.

Item 16H. Mine Safety Disclosure

Not applicable.

Item 16I. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable.

Part III

Item 17. Financial Statements

The Company has responded to Item 18 in lieu of this item.

Item 18. Financial Statements

The information required by this item is set forth in our consolidated financial statements included in this annual report.

Item 19. Exhibits

Exhibit No.	Exhibit
Exhibit 1.1	Articles of Incorporation of Takeda Pharmaceutical Company Limited (English Translation) (incorporated by reference to Exhibit 99.1 to the Registration Statement on Form 6-K of the registrant furnished on March 1, 2023)
Exhibit 1.2*	Board of Directors Charter of Takeda Pharmaceutical Company Limited (English Translation).
Exhibit 1.3	Company Share Policy of Takeda Pharmaceutical Company Limited (English Translation) (incorporated by reference to Exhibit 1.3 to the Annual Report for the Fiscal Year Ended March 31, 2022 on Form 20-F of the registrant, filed on June 29, 2022).
Exhibit 2.1	Form of Amended and Restated Deposit Agreement among the Takeda Pharmaceutical Company Limited, The Bank of New York Mellon, as Depositary, and all Owners and Holders from time to time of American Depositary Shares issued thereunder (incorporated by reference to Exhibit 2.1 to Amendment No. 1 to the Registration Statement on Form 20-F of the registrant, filed on December 17, 2018).
Exhibit 2.2	Description of the rights of each class of securities that is registered under Section 12 of the Exchange Act as of the end of the period covered by this report (incorporated by reference to Exhibit 2.2 to the Annual Report for the Fiscal Year Ended March 31, 2021 on Form 20-F of the registrant, filed on June 29, 2021).
Exhibit 4.1+	Collaboration Agreement dated December 14, 2009 by and between Seagen Inc. (f/k/a Seattle Genetics, Inc.) and Takeda Manufacturing U.S.A., Inc. (as successor in interest to Millennium Pharmaceuticals, Inc) (incorporated by reference to Exhibit 4.1 to the Annual Report for the Fiscal Year Ended March 31, 2021 on Form 20-F of the registrant, filed on June 29, 2021).
Exhibit 4.2	Amendment to Collaboration Agreement dated November 7, 2022 by and between Seagen Inc. and Takeda Manufacturing U.S.A., Inc. (incorporated by reference to Exhibit 10.2 to the Current Report of Seagen Inc. on Form 10-K filed on February 15, 2023).
Exhibit 4.3	Takeda Pharmaceutical Company Limited Long Term Incentive Plan (incorporated by reference to Exhibit 99.1 to the Registration Statement on Form S-8 of the registrant filed on June 25, 2020).
Exhibit 4.4*	Stock Purchase Agreement by and between Takeda Pharmaceuticals U.S.A., Inc. and Nimbus Therapeutics, LLC
Exhibit 8.1	List of subsidiaries of Takeda Pharmaceutical Company Limited, as of March 31, 2023: See "Item 4. Information on the Company—C. Organizational Structure."
Exhibit 12.1*	Certification of the principal executive officer required by 17 C.F.R. 240. 13a-14(a).
Exhibit 12.2*	Certification of the principal financial officer required by 17 C.F.R. 240. 13a-14(a).
Exhibit 13.1*	Certification of the chief executive officer required by 18 U.S.C. Section 1350.
Exhibit 13.2*	Certification of the chief financial officer required by 18 U.S.C. Section 1350.
Exhibit 15.1*	Consent of Independent Registered Public Accounting Firm.
101.INS*	Inline XBRL Instance Document—the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document
101.SCH*	Inline XBRL Taxonomy Extension Schema Document
101.CAL*	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF*	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB*	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE*	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104*	The cover page for the registrant's Annual Report on Form 20-F for the year ended March 31, 2023, has been formatted in Inline XBRL

* Filed herewith.

\+ Certain confidential information contained in this exhibit, marked by brackets therein, has been omitted, because it is both not material and would likely cause competitive harm if publicly disclosed.

We have not included as exhibits certain instruments with respect to our long-term debt where the amount of debt authorized under each such debt instrument does not exceed 10% or our total assets. We will furnish a copy of any such instrument to the SEC upon request.

SIGNATURES

The registrant hereby certifies that it meets all of the requirements for filing on Form 20-F and that it has duly caused and authorized the undersigned to sign this annual report on its behalf.

TAKEDA PHARMACEUTICAL COMPANY LIMITED

By: /s/ Costa Saroukos
Name: Costa Saroukos
Title: Director and Chief Financial Officer

Date: June 28, 2023

TAKEDA PHARMACEUTICAL COMPANY LIMITED AND ITS SUBSIDIARIES

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Report of Independent Registered Public Accounting Firm

To the Shareholders and Board of Directors
Takeda Pharmaceutical Company Limited:

Opinion on the Consolidated Financial Statements

We have audited the accompanying consolidated statements of financial position of Takeda Pharmaceutical Company Limited and its subsidiaries (the Company) as of March 31, 2023 and 2022, the related consolidated statements of profit or loss, comprehensive income, changes in equity, and cash flows for each of the years in the three-year period ended March 31, 2023, and the related notes (collectively, the consolidated financial statements). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of March 31, 2023 and 2022, and the results of its operations and its cash flows for each of the years in the three-year period ended March 31, 2023, in conformity with International Financial Reporting Standards as issued by the International Accounting Standards Board.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of March 31, 2023, based on criteria established in *Internal Control – Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission, and our report dated June 28, 2023 expressed an unqualified opinion on the effectiveness of the Company's internal control over financial reporting.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the consolidated financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the consolidated financial statements and (2) involved our especially challenging, subjective, or complex judgments. The communication of a critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Evaluation of the provisions for U.S. Medicaid and U.S. commercial managed care rebates

As discussed in Notes 3 and 23 to the consolidated financial statements, the Company recorded provisions for contractual and statutory rebates payable under Commercial healthcare provider contracts and U.S. State and Federal government health programs (collectively, "U.S. rebates") of 293,385 million JPY which included U.S. Medicaid and U.S. commercial managed care programs as a reduction to gross sales to arrive at net sales as of March 31, 2023. The provisions for U.S. rebates are recorded in the same period that the corresponding revenues are recognized; however, the U.S. rebates are not fully paid until subsequent periods.

We identified the evaluation of the provisions for U.S. Medicaid and U.S. commercial managed care rebates as a critical audit matter. A high degree of auditor judgement was required to evaluate the expected product specific assumptions used to estimate the provisions for the U.S. Medicaid and U.S. commercial managed care rebates. The expected product specific assumptions relate to estimating which of the Company's revenue transactions will ultimately be subject to the U.S. Medicaid and U.S. commercial managed care programs.

The following are the primary procedures we performed to address this critical audit matter. We evaluated the design and tested operating effectiveness of certain internal controls over the Company's U.S. Medicaid and U.S. commercial managed care programs provision process. This included controls related to the determination of the expected product specific assumptions used to estimate the provisions for U.S. Medicaid and U.S. commercial managed care programs. We developed independent expectations of U.S. Medicaid and U.S. commercial managed care programs provisions based on the ratios of historical U.S. Medicaid and U.S. commercial managed care programs claims paid to historical gross sales and compared the results to the Company's estimated U.S. Medicaid and U.S. commercial managed care programs provisions. We compared a selection of U.S. Medicaid and U.S. commercial managed care programs claims paid by the Company for consistency with the contractual terms of the Company's rebate agreements. We evaluated the Company's ability to accurately estimate the provisions for U.S. Medicaid and U.S. commercial managed care programs by comparing historically recorded provisions to the actual amounts that were ultimately paid by the Company.

/s/ KPMG AZSA LLC

We have served as the Company's auditor since 2007.

Tokyo, Japan
June 28, 2023

Report of Independent Registered Public Accounting Firm

To the Shareholders and Board of Directors
Takeda Pharmaceutical Company Limited:

Opinion on Internal Control Over Financial Reporting

We have audited Takeda Pharmaceutical Company Limited and its subsidiaries' (the Company) internal control over financial reporting as of March 31, 2023, based on criteria established in *Internal Control – Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission. In our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of March 31, 2023, based on criteria established in *Internal Control – Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated statements of financial position of the Company as of March 31, 2023 and 2022, the related consolidated statements of profit or loss, comprehensive income, changes in equity, and cash flows for each of the years in the three-year period ended March 31, 2023, and the related notes (collectively, the consolidated financial statements), and our report dated June 28, 2023 expressed an unqualified opinion on those consolidated financial statements.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying Management's Annual Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audit also included performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ KPMG AZSA LLC

Tokyo, Japan
June 28, 2023

TAKEDA PHARMACEUTICAL COMPANY LIMITED AND ITS SUBSIDIARIES

Consolidated Statements of Profit or Loss for the Year Ended March 31,

	Note	JPY (millions, except per share data) 2021	2022	2023
Revenue	4	¥ 3,197,812	¥ 3,569,006	¥ 4,027,478
Cost of sales		(994,308)	(1,106,846)	(1,244,072)
Selling, general and administrative expenses		(875,663)	(886,361)	(997,309)
Research and development expenses		(455,833)	(526,087)	(633,325)
Amortization and impairment losses on intangible assets associated with products	12	(421,864)	(472,915)	(542,443)
Other operating income	5	318,020	43,123	25,424
Other operating expenses	5	(258,895)	(159,075)	(145,247)
Operating profit		509,269	460,844	490,505
Finance income	6	105,521	23,700	62,913
Finance expenses	6	(248,631)	(166,607)	(169,698)
Share of profit (loss) of investments accounted for using the equity method	14	76	(15,367)	(8,630)
Profit before tax		366,235	302,571	375,090
Income tax (expenses) benefit	7	9,936	(72,405)	(58,052)
Net profit for the year		¥ 376,171	¥ 230,166	¥ 317,038
Attributable to:				
Owners of the Company	8	¥ 376,005	¥ 230,059	¥ 317,017
Non-controlling interests		166	107	21
Net profit for the year		¥ 376,171	¥ 230,166	¥ 317,038
Earnings per share (JPY)				
Basic earnings per share	8	¥ 240.72	¥ 147.14	¥ 204.29
Diluted earnings per share	8	238.96	145.87	201.94

See accompanying notes to consolidated financial statements.

TAKEDA PHARMACEUTICAL COMPANY LIMITED AND ITS SUBSIDIARIES

Consolidated Statements of Comprehensive Income for the Year Ended March 31,

	Note	JPY (millions) 2021	2022	2023
Net profit for the year		¥ 376,171	¥ 230,166	¥ 317,038
Other comprehensive income (loss)				
Items that will not be reclassified to profit or loss:				
Changes in fair value of financial assets measured at fair value through other comprehensive income	9	61,866	(14,626)	(2,654)
Remeasurement of defined benefit pension plans	9	4,866	20,783	17,752
		66,732	6,158	15,098
Items that may be reclassified subsequently to profit or loss:				
Exchange differences on translation of foreign operations	9	309,304	583,969	618,773
Cash flow hedges	9	(45,345)	2,173	(21,451)
Hedging cost	9	(9,147)	2,457	(16,993)
Share of other comprehensive loss of investments accounted for using the equity method	9, 14	(299)	(497)	(892)
		254,513	588,103	579,437
Other comprehensive income for the year, net of tax	9	321,245	594,261	594,535
Total comprehensive income for the year		¥ 697,416	¥ 824,427	¥ 911,574
Attributable to:				
Owners of the Company		¥ 697,202	¥ 824,258	¥ 911,529
Non-controlling interests		214	168	45
Total comprehensive income for the year		¥ 697,416	¥ 824,427	¥ 911,574

See accompanying notes to consolidated financial statements.

TAKEDA PHARMACEUTICAL COMPANY LIMITED AND ITS SUBSIDIARIES

Consolidated Statements of Financial Position as of March 31,

	Note	JPY (millions) 2022	2023
Assets			
Non-current assets:			
Property, plant and equipment	10	¥ 1,582,800	¥ 1,691,229
Goodwill	11	4,407,749	4,790,723
Intangible assets	12	3,818,544	4,269,657
Investments accounted for using the equity method	14	96,579	99,174
Other financial assets	15	233,554	279,683
Other non-current assets		82,611	63,325
Deferred tax assets	7	362,539	366,003
Total non-current assets		10,584,376	11,559,794
Current assets:			
Inventories	16	853,167	986,457
Trade and other receivables	17	696,644	649,429
Other financial assets	15	25,305	20,174
Income taxes receivable		27,733	32,264
Other current assets		141,099	160,868
Cash and cash equivalents	18	849,695	533,530
Assets held for sale	19	—	15,235
Total current assets		2,593,642	2,397,956
Total assets		¥ 13,178,018	¥ 13,957,750

See accompanying notes to consolidated financial statements.

	Note	JPY (millions) 2022	2023
Liabilities and Equity			
Liabilities:			
Non-current liabilities:			
Bonds and loans	20	¥ 4,141,418	¥ 4,042,741
Other financial liabilities	21	468,943	534,269
Net defined benefit liabilities	22	145,847	127,594
Income taxes payable		21,634	24,558
Provisions	23	52,199	55,969
Other non-current liabilities	24	67,214	65,389
Deferred tax liabilities	7	451,511	270,620
Total non-current liabilities		5,348,764	5,121,138
Current liabilities:			
Bonds and loans	20	203,993	339,600
Trade and other payables	25	516,297	649,233
Other financial liabilities	21	196,071	185,537
Income taxes payable		200,918	232,377
Provisions	23	443,502	508,360
Other current liabilities	24	584,949	566,689
Liabilities held for sale	19	—	144
Total current liabilities		2,145,730	2,481,940
Total liabilities		7,494,495	7,603,078
Equity:			
Share capital		1,676,263	1,676,345
Share premium		1,708,873	1,728,830
Treasury shares		(116,007)	(100,317)
Retained earnings		1,479,716	1,541,146
Other components of equity		934,173	1,508,119
Equity attributable to owners of the Company		5,683,019	6,354,122
Non-controlling interests		504	549
Total equity		5,683,523	6,354,672
Total liabilities and equity		¥ 13,178,018	¥ 13,957,750

See accompanying notes to consolidated financial statements.

TAKEDA PHARMACEUTICAL COMPANY LIMITED AND ITS SUBSIDIARIES

Consolidated Statements of Changes in Equity

JPY (millions)

	Equity attributable to owners of the Company												
					Other components of equity								
	Share capital	Share premium	Treasury shares	Retained earnings	Exchange differences on translation of foreign operations	Changes in fair value of financial assets measured at fair value through other comprehensive income	Cash flow hedges	Hedging cost	Remeasurements of defined benefit pension plans	Total other components of equity	Total equity attributable to owners of the Company	Non-controlling interests	Total equity
As of April 1, 2020	¥ 1,668,123	¥ 1,680,287	¥ (87,463)	¥ 1,369,972	¥ 91,848	¥ 22,891	¥ (22,730)	¥ 555	¥ —	¥ 92,564	¥ 4,723,483	¥ 4,003	¥ 4,727,486
Net profit for the year				376,005						—	376,005	166	376,171
Other comprehensive income (loss)					308,950	61,873	(45,345)	(9,147)	4,866	321,197	321,197	48	321,245
Comprehensive income (loss) for the year	—	—	—	376,005	308,950	61,873	(45,345)	(9,147)	4,866	321,197	697,202	214	697,416
Transactions with owners:													
Issuance of new shares	22	22								—	44		44
Acquisition of treasury shares			(2,141)							—	(2,141)		(2,141)
Disposal of treasury shares		(0)	2							—	2		2
Dividends (Note 26)				(283,718)						—	(283,718)	(77)	(283,795)
Transfers from other components of equity				47,647		(42,781)			(4,866)	(47,647)	—		—
Share-based compensation (Note 28)		37,663								—	37,663		37,663
Exercise of share-based awards (Note 28)		(29,548)	30,050							—	502		502
Total transactions with owners	22	8,137	27,911	(236,071)	—	(42,781)	—	—	(4,866)	(47,647)	(247,648)	(77)	(247,725)
As of March 31, 2021	¥ 1,668,145	¥ 1,688,424	¥ (59,552)	¥ 1,509,906	¥ 400,798	¥ 41,983	¥ (68,075)	¥ (8,592)	¥ —	¥ 366,114	¥ 5,173,037	¥ 4,140	¥ 5,177,177

See accompanying notes to consolidated financial statements.

TAKEDA PHARMACEUTICAL COMPANY LIMITED AND ITS SUBSIDIARIES

Consolidated Statements of Changes in Equity

	JPY (millions)											
	Equity attributable to owners of the Company											
					Other components of equity							
	Share capital	Share premium	Treasury shares	Retained earnings	Exchange differences on translation of foreign operations	Changes in fair value of financial assets measured at fair value through other comprehensive income	Cash flow hedges	Hedging cost	Remeasurements of defined benefit pension plans	Total other components of equity	Total equity attributable to owners of the Company	Non-controlling interests	Total equity
As of April 1, 2021	¥ 1,668,145	¥ 1,688,424	¥ (59,552)	¥ 1,509,906	¥ 400,798	¥ 41,983	¥ (68,075)	¥ (8,592)	¥ —	¥ 366,114	¥ 5,173,037	¥ 4,140	¥ 5,177,177
Net profit for the year				230,059						—	230,059	107	230,166
Other comprehensive income (loss)					583,343	(14,558)	2,173	2,457	20,783	594,200	594,200	61	594,261
Comprehensive income (loss) for the year	—	—	—	230,059	583,343	(14,558)	2,173	2,457	20,783	594,200	824,258	168	824,427
Transactions with owners:													
Issuance of new shares (Note 26)	8,118	14,036								—	22,154		22,154
Acquisition of treasury shares (Note 26)			(79,447)							—	(79,447)		(79,447)
Disposal of treasury shares		(0)	1							—	1		1
Dividends (Note 26)				(284,246)						—	(284,246)		(284,246)
Changes in ownership				(2,143)						—	(2,143)	(3,804)	(5,948)
Transfers from other components of equity				26,141		(5,357)			(20,783)	(26,141)	—		—
Share-based compensation (Note 28)		43,374								—	43,374		43,374
Exercise of share-based awards (Note 28)		(36,960)	22,992							—	(13,968)		(13,968)
Total transactions with owners	8,118	20,450	(56,454)	(260,249)	—	(5,357)	—	—	(20,783)	(26,141)	(314,276)	(3,804)	(318,080)
As of March 31, 2022	¥ 1,676,263	¥ 1,708,873	¥ (116,007)	¥ 1,479,716	¥ 984,141	¥ 22,068	¥ (65,901)	¥ (6,135)	¥ —	¥ 934,173	¥ 5,683,019	¥ 504	¥ 5,683,523

See accompanying notes to consolidated financial statements.

TAKEDA PHARMACEUTICAL COMPANY LIMITED AND ITS SUBSIDIARIES

Consolidated Statements of Changes in Equity

	JPY (millions)											
	Equity attributable to owners of the Company											
					Other components of equity							
	Share capital	Share premium	Treasury shares	Retained earnings	Exchange differences on translation of foreign operations	Changes in fair value of financial assets measured at fair value through other comprehensive income	Cash flow hedges	Hedging cost	Remeasurements of defined benefit pension plans	Total other components of equity	Total equity attributable to owners of the Company	Non-controlling interests	Total equity
As of April 1, 2022	¥ 1,676,263	¥ 1,708,873	¥ (116,007)	¥ 1,479,716	¥ 984,141	¥ 22,068	¥ (65,901)	¥ (6,135)	¥ —	¥ 934,173	¥ 5,683,019	¥ 504	¥ 5,683,523
Effect of hyperinflation				(1,960)	4,121					4,121	2,161		2,161
Restated opening balance	1,676,263	1,708,873	(116,007)	1,477,756	988,263	22,068	(65,901)	(6,135)	—	938,294	5,685,180	504	5,685,684
Net profit for the year				317,017						—	317,017	21	317,038
Other comprehensive income (loss)					617,866	(2,663)	(21,451)	(16,993)	17,752	594,512	594,512	24	594,535
Comprehensive income (loss) for the year	—	—	—	317,017	617,866	(2,663)	(21,451)	(16,993)	17,752	594,512	911,529	45	911,574
Transactions with owners:													
Issuance of new shares (Note 26)	82	82								—	164		164
Acquisition of treasury shares (Note 26)		(5)	(27,060)							—	(27,065)		(27,065)
Disposal of treasury shares		0	0							—	1		1
Dividends (Note 26)				(278,313)						—	(278,313)		(278,313)
Transfers from other components of equity				24,687		(6,935)			(17,752)	(24,687)	—		—
Share-based compensation (Note 28)		62,670								—	62,670		62,670
Exercise of share-based awards (Note 28)		(42,791)	42,749							—	(42)		(42)
Total transactions with owners	82	19,956	15,689	(253,626)	—	(6,935)	—	—	(17,752)	(24,687)	(242,586)	—	(242,586)
As of March 31, 2023	¥ 1,676,345	¥ 1,728,830	¥ (100,317)	¥ 1,541,146	¥ 1,606,128	¥ 12,470	¥ (87,352)	¥ (23,127)	¥ —	¥ 1,508,119	¥ 6,354,122	¥ 549	¥ 6,354,672

See accompanying notes to consolidated financial statements.

TAKEDA PHARMACEUTICAL COMPANY LIMITED AND ITS SUBSIDIARIES

Consolidated Statements of Cash Flows for the Year Ended March 31,

	Note	JPY (millions) 2021	2022	2023
Cash flows from operating activities:				
Net profit for the year		¥ 376,171	¥ 230,166	¥ 317,038
Depreciation and amortization		559,671	583,151	664,400
Impairment losses		25,452	54,515	64,394
Equity-settled share-based compensation		37,663	43,374	60,672
Change in estimate of liabilities related to SHP647	5	(60,179)	—	—
Loss (gain) on sales and disposal of property, plant and equipment		(2,109)	655	10
Gain on divestment of business and subsidiaries		(229,993)	(7,829)	(6,807)
Change in fair value of financial assets and liabilities associated with contingent consideration arrangements, net		59,277	(11,195)	3,991
Finance (income) and expenses, net		143,110	142,907	106,785
Share of loss (profit) of investments accounted for using the equity method		(76)	15,367	8,630
Income tax expenses (benefit)		(9,936)	72,405	58,052
Changes in assets and liabilities:				
Decrease (increase) in trade and other receivables		(9,316)	127,294	75,127
Decrease (increase) in inventories		25,978	(46,148)	(79,155)
Increase (decrease) in trade and other payables		36,620	125,157	(84,804)
Increase (decrease) in provisions		49,099	(58,090)	31,899
Increase (decrease) in other financial liabilities		173,400	(49,608)	31,669
Other, net		37,786	41,409	(88,778)
Cash generated from operations		1,212,618	1,263,528	1,163,122
Income taxes paid		(235,801)	(147,724)	(198,439)
Tax refunds and interest on tax refunds received		34,114	7,301	12,473
Net cash from operating activities		1,010,931	1,123,105	977,156
Cash flows from investing activities:				
Interest received		1,105	2,919	5,054
Dividends received		387	3,401	3,562
Acquisition of property, plant and equipment		(111,206)	(123,252)	(140,657)
Proceeds from sales of property, plant and equipment		46,453	1,815	962
Acquisition of intangible assets		(125,262)	(62,785)	(493,032)
Acquisition of investments		(12,596)	(8,341)	(10,151)
Proceeds from sales and redemption of investments		74,604	16,921	22,254
Acquisition of businesses, net of cash and cash equivalents acquired		—	(49,672)	—
Proceeds from sales of business, net of cash and cash equivalents divested		530,388	28,196	7,958
Other, net		(10,343)	(7,328)	(3,052)
Net cash from (used in) investing activities		393,530	(198,125)	(607,102)
Cash flows from financing activities:				
Net increase (decrease) in short-term loans and commercial papers	27	(149,043)	(2)	40,000
Proceeds from issuance of bonds and long-term loans	27	1,179,515	249,334	75,000
Repayments of bonds and long-term loans	27	(1,651,706)	(810,115)	(356,670)
Payments for settlement of forward rate agreement related to bonds		(34,830)	—	—
Acquisition of treasury shares		(2,141)	(77,531)	(26,929)
Interest paid		(107,350)	(108,207)	(108,555)
Dividends paid		(283,357)	(283,665)	(279,416)
Repayments of lease liabilities	27	(39,270)	(39,694)	(43,401)
Other, net		(172)	(385)	(9,178)
Net cash used in financing activities		(1,088,354)	(1,070,265)	(709,148)
Net increase (decrease) in cash and cash equivalents		316,107	(145,285)	(339,094)
Cash and cash equivalents at the beginning of the year	18	637,614	966,222	849,695
Effects of exchange rate changes on cash and cash equivalents		12,501	28,758	22,929
Cash and cash equivalents at the end of the year	18	966,222	849,695	533,530

See accompanying notes to consolidated financial statements.

TAKEDA PHARMACEUTICAL COMPANY LIMITED AND ITS SUBSIDIARIES

Notes to Consolidated Financial Statements

1. Reporting Entity

Takeda Pharmaceutical Company Limited (the "Company") is a public company incorporated in Japan. The Company and its subsidiaries (collectively, "Takeda") is a global, values-based, R&D-driven biopharmaceutical company with a diverse portfolio, engaged primarily in the research, development, production and global commercialization of pharmaceutical products. Takeda's principal pharmaceutical products include medicines in the following key business areas: gastroenterology ("GI"), rare diseases, Plasma-Derived Therapies ("PDT") immunology, oncology, and neuroscience.

2. Basis of Preparation

Compliance with International Financial Reporting Standards

Takeda's consolidated financial statements have been prepared in accordance with International Financial Reporting Standards ("IFRS"), as issued by the International Accounting Standards Board ("IASB"). The term IFRS also includes International Accounting Standards ("IASs") and the related interpretations of the interpretation's committees (Standard Interpretations Committee ("SIC") and International Financial Reporting Interpretations Committee ("IFRIC")).

Approval of Financial Statements

The Company's consolidated financial statements presented were approved on June 28, 2023 by Representative Director, President & Chief Executive Officer ("CEO") Christophe Weber and Director & Chief Financial Officer ("CFO") Costa Saroukos.

Basis of Measurement

The consolidated financial statements have been prepared on a historical cost basis, except for certain assets and liabilities recorded at fair value including equity investments, derivative financial instruments, financial assets and liabilities associated with contingent consideration arrangements, and the application of hyperinflationary accounting at subsidiaries.

Functional and Presentation Currency

The consolidated financial statements are presented in Japanese Yen ("JPY"), which is the functional currency of the Company. All financial information presented in JPY has been rounded to the nearest million JPY, except when otherwise indicated. In tables with rounded figures, sums may not add up due to rounding.

New Accounting Standards and Interpretations Adopted

During the year ended March 31, 2023, there were no new accounting standards applied by Takeda that had a significant impact on Takeda's consolidated financial statements.

New Accounting Standards and Interpretations Issued and Not Yet Adopted

On May 23, 2023, amendments to IAS 12 *Income Taxes* ("IAS12") were issued to clarify requirements relating to the International Tax Reform - Pillar Two model rules. As required by the amended IAS12, Takeda adopted immediately and retrospectively the exception to neither recognize nor disclose information about deferred tax assets and liabilities related to Pillar Two model rules. The amended IAS12 requirements to provide new disclosures regarding the exposure of Pillar Two model rules to the consolidated financial statements are applicable to Takeda from the fiscal year beginning April 1, 2023.

Use of Judgments, Estimates, and Assumptions

The preparation of consolidated financial statements in accordance with IFRS requires management to make certain judgments, estimates, and assumptions that affect the application of accounting policies and the reported amount of assets, liabilities, revenues and expenses, and the disclosure of contingent assets and liabilities. Actual results could differ from these estimates.

These estimates and underlying assumptions are reviewed on a continuous basis. Changes in these accounting estimates are recognized in the period in which the estimates are revised and in any future periods affected.

Information about judgments and estimates that have been made in the process of applying accounting policies and that have significant effects on the amounts reported in the consolidated financial statements, and information about accounting estimates and assumptions that have significant effects on the amounts reported in the consolidated financial statements, are as follows:

- Recognition and measurement of taxes based on uncertain tax positions (Note 7)
- Recoverability of deferred tax assets (Note 7)
- Impairment of goodwill and intangible assets (Note 11 and Note 12)
- Measurement of provisions (Note 23)
- Estimation of rebates and return reserves associated with Takeda's product sales (Note 3 and Note 23)
- Probability of an outflow of resources embodying economic benefits on contingent liabilities (Note 32)

Although the COVID-19 pandemic could potentially impact business activities within Takeda, the overall impact on Takeda's consolidated financial results has been limited to date. Therefore, the pandemic did not have a significant impact on accounting estimates and assumptions used for the preparation of the consolidated financial statements. Takeda will continue to reassess estimates and assumptions as the situation evolves.

3. Significant Accounting Policies

Basis of Consolidation

The consolidated financial statements include the accounts of the Company and its subsidiaries that are directly or indirectly controlled by the Company. All significant intercompany balances and transactions have been eliminated in consolidation.

Takeda controls an entity when it is exposed or has rights to variable returns from involvement with the entity and has the ability to affect those returns using its power, which is the current ability to direct the relevant activities, over the entity. To determine whether Takeda controls an entity, status of voting rights or similar rights, contractual agreements and other specific factors are considered.

The financial statements of the subsidiaries are included in the consolidated financial statements from the date when control is obtained until the date when control is lost. The financial statements of subsidiaries have been adjusted in order to ensure consistency with the accounting policies adopted by the Company as necessary.

Changes in ownership interest in subsidiaries that do not result in loss of control are accounted for as equity transactions. Any difference between the adjustment to non-controlling interests and the fair value of consideration transferred or received, is recognized directly in equity attributable to owners of the Company. When control over a subsidiary is lost, the investment retained after the loss of control is re-measured at fair value as of the date when control is lost, and any gain or loss on such re-measurement and disposal of the interest sold is recognized in profit or loss.

Investments in Associates and Joint Arrangements

Associates are entities over which Takeda has significant influence over the decisions on financial and operating policies but does not have control or joint control. Investments in associates are accounted for using the equity method and recognized at cost on the acquisition date. The carrying amount is subsequently increased or decreased to recognize Takeda's share of profit or loss and other comprehensive income of the associates. Intra-group profits on transactions with associates accounted for using the equity method are eliminated against the investment to the extent of Takeda's equity interest in the associates. Intra-group losses are eliminated in the same way as intra-group profits unless there is evidence of impairment.

Joint arrangement is an arrangement of which two or more parties have joint control. Joint control is the contractually agreed sharing of control of an arrangement, which exists only when decisions about the relevant activities require the unanimous consent of the parties sharing control. Takeda classifies joint arrangement into either joint operations or joint ventures. The classification of a joint arrangement as a joint operation or a joint venture depends upon the rights and obligations of the parties to the arrangement. Joint operation is a joint arrangement whereby the parties that have joint control of the arrangement have rights to the assets, and obligations for the liabilities, relating to the arrangement. Joint venture is a joint arrangement whereby the parties that have joint control of the arrangement have rights to the net assets of the arrangement. The assets, liabilities, revenues and expenses in joint operations are recognized in relation to Takeda's interest. The investment in joint ventures is accounted for using the equity method. At each reporting date, the Company determines whether there is objective evidence that the investment in the associate or joint venture is impaired. If there is such evidence, the Company calculates the amount of impairment as the difference between the recoverable amount of the associate or joint venture and its carrying value, and then recognizes the loss in profit or loss.

Business Combinations

Business combinations are accounted for using the acquisition method. The identifiable assets acquired and the liabilities assumed are measured at the fair values at the acquisition date. Goodwill is measured as the excess of the sum of the fair value of consideration transferred, the amount of any non-controlling interests in the acquiree and the fair value of the acquirer's previously held equity interest in the acquiree less the fair value of identifiable assets acquired, net of liabilities assumed at the acquisition date. As part of business combinations, when the acquired entity consists of foreign operations with multiple functional currencies, Takeda allocates goodwill recognized upon the acquisition to the foreign operations based on the estimated cash flows of the acquired foreign operations.

The consideration transferred for the acquisition of a subsidiary is measured as the fair value of the assets transferred, the liabilities incurred to former owners of the acquiree, and the equity interests issued by Takeda at the acquisition date. Non-controlling interests is initially measured either at fair

value or at the non-controlling interests' proportionate share of the recognized amounts of the acquiree's identifiable net assets on a transaction-by-transaction basis. The consideration for certain acquisitions includes amounts contingent upon future events, such as the achievement of development milestones and sales targets.

Any contingent consideration included in the consideration payable for a business combination is recorded at fair value at the date of acquisition. These fair values are generally based on risk-adjusted future cash flows discounted using appropriate discount rates. The fair values are reviewed at the end of each reporting period. The changes in the fair value based on the time value of money are recognized in finance expenses and the other changes are recognized in other operating income or other operating expenses in the consolidated statements of profit or loss.

Acquisition related costs are recognized as expenses in the period they are incurred. Changes in Takeda's ownership interests in subsidiaries arising from transactions between Takeda and non-controlling interests that do not result in Takeda losing control over a subsidiary are treated as equity transactions and therefore, do not result in adjustments to goodwill.

Foreign Currency Translations

Foreign Currency Transactions

Foreign currency transactions are remeasured into the functional currency of each entity within Takeda using the exchange rates at the dates of the transactions or rates that approximate the exchange rates at the dates of the transactions. Monetary assets and liabilities denominated in foreign currencies are remeasured into the functional currency using the spot rates of exchange at the end of each reporting period. Non-monetary assets and liabilities that are measured at fair value in foreign currencies are remeasured using historical exchange rates at the date when the fair value was determined. Non-monetary assets and liabilities measured based on historical cost that are denominated in foreign currencies are remeasured at the exchange rate at the date of the initial transaction. Exchange differences arising from the remeasurement or settlement are recognized in profit or loss except when related to financial assets measured at fair value through other comprehensive income, as well as financial instruments designated as hedges of net investments in foreign operations and cash flow hedges subsequently recognized as other comprehensive income. The gain or loss arising from remeasurement of non-monetary items measured at fair value is treated in line with the recognition of the gain or loss on the change in fair value of the item (i.e., translation differences on items whose fair value gain or loss is recognized in other comprehensive income or profit or loss, are also recognized in other comprehensive income or profit or loss, respectively).

Foreign Operations

The assets and liabilities of foreign operations are translated using the spot exchange rates at the end of the reporting period, while income and expenses of foreign operations presented in profit or loss and other comprehensive income are translated using the exchange rates at the dates of the transactions or rates that approximate the exchange rates at the dates of the transactions. When a foreign operation's functional currency is the currency of a hyperinflationary economy, adjustments are made to its separate financial statements to reflect current price levels, and income and expenses of the foreign operation are translated into the presentation currency at the exchange rate at the end of the reporting period. The impact of the restatement of the non-monetary assets and liabilities with the general price index at the beginning of the period is recorded in other comprehensive income.

Exchange differences arising from translation are recognized as other comprehensive income. In cases in which foreign operations are disposed of, the cumulative amount of exchange differences related to the foreign operations is recognized as part of the gain or loss on disposal.

Revenue

Takeda's revenue is primarily related to the sale of pharmaceutical products and is generally recognized when control of the products is passed to the customer in an amount that reflects the consideration to which Takeda expects to be entitled in exchange for those products. Control is generally transferred at the point in time of shipment to or receipt of the products by the customer, or when the services are performed. The amount of revenue to be recognized is based on the consideration Takeda expects to receive in exchange for its goods or services. If a contract contains more than one contractual promise to a customer (performance obligation), the consideration is allocated based on the standalone selling price of each performance obligation. The consideration Takeda receives in exchange for its goods or services may be fixed or variable. Variable consideration is only recognized to the extent it is highly probable that a significant reversal will not occur.

Takeda's gross sales are subject to various deductions, which are primarily composed of rebates and discounts to retail customers, government agencies, wholesalers, health insurance companies and managed healthcare organizations. These deductions represent estimates of the related obligations, requiring the use of judgment when estimating the effect of these sales deductions on gross sales for a reporting period. These adjustments are deducted from gross sales to arrive at net sales. Takeda monitors the obligation for these deductions on at least a quarterly basis and records adjustments when rebate trends, rebate programs and contract terms, legislative changes, or other significant events indicate that a change in the obligation is appropriate. Historically, adjustments to rebate accruals have not been material to net earnings. The United States (the "U.S.") market has the most complex arrangements related to revenue deductions.

The following summarizes the nature of the most significant adjustments to revenue:

- U.S. Medicaid: The U.S. Medicaid Drug Rebate Program is administered by state governments using state and federal funds to provide assistance to certain qualifying individuals and families, who cannot finance their own medical expenses. Calculating the rebates to be paid related to this program involves interpreting relevant regulations, which are subject to challenge or change in interpretative guidance by

government authorities. Provisions for Medicaid rebates are estimated based upon identifying the products subject to a rebate, historical experience, patient demand, product pricing and the mix of contracts and specific terms in the individual state agreements. The provisions for Medicaid rebates are recorded in the same period that the corresponding revenues are recognized; however, the Medicaid rebates are not fully paid until subsequent periods. There is often a time lag of several months between Takeda recording the revenue deductions and Takeda's final accounting for Medicaid rebates. These expected product specific assumptions relate to estimating which of Takeda's revenue transactions will ultimately be subject to the U.S. Medicaid program.

- U.S. Medicare: The U.S. Federal Medicare Program, which funds healthcare benefits to individuals age 65 or older and certain disabilities, provides prescription drug benefits under Part D section of the program. This benefit is provided and administrated through private prescription drug plans. Provisions for Medicare Part D rebates are calculated based on the terms of individual plan agreements, patient demand, product pricing and the mix of contracts. The provisions for Medicare Part D rebates are recorded in the same period that the corresponding revenues are recognized; however, the Medicare Part D rebates are not fully paid until subsequent periods. There is often a time lag of several months between Takeda recording the revenue deductions and Takeda's final accounting for Medicare Part D rebates. These expected product specific assumptions relate to estimating which of the Takeda's revenue transactions will ultimately be subject to the U.S. Medicare program.
- Customer rebates: Customer rebates including commercial managed care in the U.S. are offered to purchasing organizations, health insurance companies, managed healthcare organizations, and other direct and indirect customers to sustain and increase market share, and to ensure patient access to Takeda's products. Since rebates are contractually agreed upon, the related provisions are estimated based on the terms of the individual agreements, historical experience, and patient demand. The provisions for commercial managed care rebates in the U.S. are recorded in the same period that the corresponding revenues are recognized; however, commercial managed care rebates in the U.S. are not fully paid until subsequent periods. There is often a time lag of several months between Takeda recording the revenue deductions and Takeda's final accounting for commercial managed care rebates in the U.S. These expected product specific assumptions relate to estimating which of Takeda's revenue transactions will ultimately be subject to the commercial managed care in the U.S.
- Wholesaler chargebacks: Takeda has arrangements with certain indirect customers whereby the customer is able to buy products from wholesalers at reduced prices. A chargeback represents the difference between the invoice price to the wholesaler and the indirect customer's contractual discounted price. Provisions for estimating chargebacks are calculated based on the terms of each agreement, historical experience and product demand. Takeda has a legally enforceable right to set off the trade receivables and chargebacks and it intends either to settle them on a net basis or to realize the asset and settle the liability simultaneously. Thus the provision for chargebacks are recorded as a deduction from trade receivables on the consolidated statements of financial position.
- Return reserves: When Takeda sells a product providing a customer with the right to return, Takeda records a provision for estimated sales returns based on its sales return policy and historical return rates. Takeda estimates the proportion of recorded revenue that will result in a return by considering relevant factors, including past product returns activity, the estimated level of inventory in the distribution channel and the shelf life of products.

Because the amounts are estimated, they may not fully reflect the final outcome, and the amounts are subject to change dependent upon, amongst other things, expected product specific assumptions used in estimating which of Takeda's revenue transactions will ultimately be subject to the respective programs.

Takeda generally receives payments from customers within 90 days after the point in time when goods are delivered to the customers. Takeda usually performs those transactions as a principal, but Takeda also sells products on behalf of others in which case revenue is recognized at an amount of sales commission that Takeda expects to be entitled as an agent.

Takeda also generates revenue in the form of royalty payments, upfront payments, and milestone payments from the out-licensing and sale of intellectual property ("IP"). Royalty revenue earned through a license is recognized when the underlying sales have occurred. Revenue from upfront payment is generally recognized when Takeda provides a right to use IP. Revenue from milestone payments is recognized at the point in time when it is highly probable that the respective milestone event criteria is met, and a significant reversal in the amount of revenue recognized will not occur. Revenue from other services such as R&D of therapeutic candidates that are out-licensed is recognized over the service period.

Takeda generally receives payments from customers within 60 days after entering into out-licensing contracts or confirmation by customers that conditions for the milestone payments are met. Takeda licenses its own intellectual property rights to customers and performs those transactions as a principal. Takeda also provides other services as a principal or an agent.

Takeda identifies a contract modification in case of a change in the scope or price (or both) of a contract. If a contract modification is not accounted for as a separate contract, both of the revenue recognized before and after contract modification is presented in the same categories of the disaggregation of revenue information.

Government Grants

Government grants are recognized when there is reasonable assurance that Takeda will comply with the conditions attached to them and receive the grants. Government grants for the purchasing of property, plant and equipment are recognized as deferred income and then recognized in profit or loss and offset the related expenses on a systematic basis over the useful lives of the related assets. Government grants for expenses incurred are recognized in profit or loss and offset the related expenses over the periods in which Takeda recognizes costs for which the grants are intended to compensate.

Research and Development Expenses

Research costs are expensed in the period incurred. Internal development expenditures are capitalized when the criteria for recognizing an asset are met in accordance with IAS 38 *Intangible Assets*, usually when a regulatory filing has been made in a major market and approval is considered highly probable. Where regulatory and other uncertainties are such that the criteria are not met, the expenditures are recognized in profit or loss in the consolidated statements of profit or loss. Property, plant and equipment used for R&D is capitalized and depreciated over the estimated life of the asset.

Income Taxes

Income taxes consist of current taxes and deferred taxes. Current and deferred taxes are recognized in profit or loss, except for income taxes resulting from business combinations, and income taxes recognized in either other comprehensive income or equity related to items that are recognized, in the same or different period, outside of profit or loss.

Current Taxes

The current taxes payable or receivable is based on taxable profit for the year. Taxable profit differs from reported profit because taxable profit excludes items that are either never taxable or tax deductible or items that are taxable or tax deductible in a different period. Income taxes payable and income taxes receivable, including those from prior fiscal years, are measured at the amount that is expected to be paid to or received from the taxation authorities using tax rates and tax law that have been enacted or substantively enacted by the reporting date, reflecting uncertainty related to income taxes, if any. Takeda's current taxes also include liabilities related to uncertain tax positions. Inherent uncertainties exist in estimates of many uncertain tax positions due to changes in tax law resulting from legislation, regulation, and/or as concluded through the various jurisdictions' tax court systems. When Takeda concludes that it is not probable that a tax authority will accept an uncertain tax position, Takeda recognizes the best estimate of the expenditure required to settle a tax uncertainty. This is measured either based on the most likely amount or the expected value amount, depending on which method provides a better prediction of the resolution of the uncertainty. The amount of unrecognized tax benefits is adjusted for changes in facts and circumstances. Takeda's current tax assets and liabilities are calculated using tax rates that have been enacted or substantively enacted by the reporting date.

Deferred Taxes

Deferred taxes are calculated based on the temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for taxation purposes at the end of the reporting period. Deferred tax assets are recognized for deductible temporary differences, unused tax credits and unused tax losses to the extent that it is probable that future taxable profit will be available against which the assets can be utilized. This requires Takeda to evaluate and assess the probability of future taxable profit and Takeda's business plan, which are inherently uncertain. The change in judgment upon determining the revenue forecast used for Takeda's business plan could have a significant impact on the amount of the deferred tax assets to be recognized. Uncertainty of estimates of future taxable profit could increase due to changes in economies in which Takeda operates, changes in market conditions, effects of currency fluctuations, or other factors. Takeda's deferred taxes also include liabilities related to uncertain tax positions. Deferred tax liabilities are generally recognized for taxable temporary differences.

Deferred tax assets and liabilities are not recognized for the following temporary differences:

- Taxable temporary differences arising on the initial recognition of goodwill
- The initial recognition of assets and liabilities in transactions that are not business combinations and affect neither accounting profit nor taxable profit (loss) at the time of the transaction
- Deductible temporary differences arising from investments in subsidiaries and associates, when it is not probable that the temporary differences will reverse in the foreseeable future and that taxable profit will be available against which the temporary differences can be utilized
- Taxable temporary differences arising from investments in subsidiaries and associates when the timing of the reversal of the temporary differences is controllable and it is not probable that they will reverse in the foreseeable future

Further, Takeda has not recognized nor disclosed deferred tax assets and liabilities of income taxes relating to the Pillar Two model's rules published by the Organization for Economic Cooperation and Development ("OECD") , as required by IAS 12 as amended on May 23, 2023.

Deferred tax assets and liabilities are measured at the tax rates that are expected to apply to the periods in which the temporary differences are expected to reverse based on the tax rates and tax laws that have been enacted or substantively enacted by the end of the reporting period. Deferred tax assets and liabilities are offset when there is a legally enforceable right to offset current tax assets against current tax liabilities and the deferred tax assets and liabilities for those related to income taxes levied by the same taxation authority on the same taxable entity.

Earnings per Share

Basic earnings per share is calculated by dividing profit or loss for the year attributable to owners of ordinary shares of the Company, by the weighted-average number of ordinary shares outstanding during the reporting period, adjusted by the number of treasury shares. Diluted earnings per share is calculated by adjusting all the effects of dilutive potential ordinary shares.

Property, Plant and Equipment

Property, plant and equipment are measured using the cost model and is stated at cost less accumulated depreciation and accumulated impairment loss. Acquisition cost includes mainly the costs directly attributable to the acquisition and the initial estimated dismantlement, removal, and restoration costs associated with the asset. Except for assets that are not subject to depreciation, such as land and construction in progress, assets are depreciated mainly using the straight-line method over the estimated useful life of the asset. Right of use ("ROU") assets are depreciated using the straight-line method over the shorter of the lease term or the estimated useful life unless it is reasonably certain that Takeda will obtain ownership by the end of the lease term. The depreciation of these assets begins when they are available for use.

The estimated useful life of major asset items is as follows:

- Buildings and structures 3 to 50 years
- Machinery and vehicles 2 to 20 years
- Tools, furniture and fixtures 2 to 20 years

Goodwill

Goodwill arising from business combinations is stated at its cost less accumulated impairment losses. Goodwill is not amortized. Goodwill is allocated to cash-generating units (CGUs) or groups of cash-generating units that represent the lowest level within the entity for which information about goodwill is available and monitored for internal management purposes and are not larger than an operating segment. Goodwill is only allocated to CGUs or groups of CGUs that are expected to benefit from synergies related to the business combination from which goodwill arose and the method of allocation depends on the facts and circumstances of the business combination. Goodwill is tested for impairment annually and whenever there is any indication of impairment. Impairment losses on goodwill are recognized in the consolidated statements of profit or loss and no subsequent reversal will be made.

Intangible Assets Associated with Products

Marketed Products

An intangible asset associated with a marketed product is amortized on a straight-line basis over the estimated useful life, which is based on expected patent life, and/or other factors depending on the expected economic benefits of the asset, ranging from 3 to 20 years. Amortization of intangible assets is included in amortization and impairment losses on intangible assets associated with products in the consolidated statements of profit or loss. Amortization and impairment losses on intangible assets associated with products is separately stated in the consolidated statements of profit or loss because intangible assets associated with products have various comprehensive rights and contribute to our ability to sell, manufacture, research, market and distribute products, compounds and benefit multiple business functions.

In-Process R&D

Takeda regularly enters into collaboration and in-license agreements with third parties for products and compounds for R&D projects. Payments for collaboration agreements generally take the form of subsequent development milestone payments. Payments for in-license agreements generally take the form of up-front payments and subsequent development milestone payments.

Up-front payments for in-license agreements are capitalized upon commencement of the in-license agreements, and development milestone payments are capitalized when the milestone is achieved.

These intangible assets relating to products in development that are not yet available for use are not amortized. These intangible assets are assessed for impairment on an annual basis, or more frequently if indicators of a potential impairment exist. An impairment is recorded if the carrying value exceeds the recoverable amount of the intangible assets. Intangible assets relating to products which fail during development or for which development ceases for any reason are written down to their recoverable amount which is typically nil.

If and when Takeda obtains approval for the commercial application of a product in development, the related in-process R&D assets will be reclassified to intangible assets associated with marketed products and amortized over its estimated useful life from marketing approval.

Intangible Assets – Software

Software is recognized at cost and amortized on a straight-line basis over the expected useful life. The useful life used for this purpose is 3 to 10 years. Amortization of intangible assets – software is included in cost of sales, selling, general and administrative expenses, and research and development expenses in the consolidated statements of profit or loss.

Leases

As Lessee

Takeda assesses whether a contract is or contains a lease at inception of a contract. As a lessee, Takeda recognizes a ROU asset and a corresponding lease liability for all contracts in which it is a lessee in the consolidated statements of financial position at the lease commencement date.

The ROU asset is initially measured at cost, being the initial amount of the lease liability adjusted for any lease payments made at or before the lease commencement date and subsequently at cost less any accumulated depreciation and impairment losses. The ROU asset is subsequently depreciated using the straight-line method over the shorter of the lease term or the estimated useful life of the underlying asset. The ROU asset is subject to impairment assessment.

The lease liability is initially measured at the present value of the lease payments that are not paid at the commencement date, discounted using the interest rate implicit in the lease or, if not readily determinable, the Takeda's incremental borrowing rate.

Generally, Takeda uses its incremental borrowing rate as the discount rate. The lease term comprises a non-cancellable period of lease contracts and periods covered by an option to extend or terminate the lease if Takeda is reasonably certain to exercise that option. After initial recognition, the lease liability is measured at amortized cost using the effective interest method. If there is a change in future lease payments, such as from reassessment of whether an extension or termination option will be exercised, the lease liability is remeasured. A corresponding adjustment is made to the ROU asset or is recorded in the consolidated statements of profit or loss when the right-of-use asset has been fully depreciated.

Takeda has elected to apply recognition exemption for leases that have a lease term of 12 months or less and leases of low-value assets. The lease payments for such leases are recognized as an expense on a straight-line basis over the lease term.

As a practical expedient, Takeda has elected not to separate non-lease components from lease components, and instead accounts for each lease component and any associated non-lease components as a single lease component.

Impairment of Non-Financial Assets

Takeda assesses whether there is any indication of impairment for non-financial assets at the end of each reporting period, excluding inventories, deferred tax assets, assets held for sale, and net defined benefit assets. If any such indication exists, or in cases in which an impairment test is required to be performed each year, the recoverable amount of the asset is estimated. In cases the recoverable amount cannot be estimated for each asset, they are estimated at the cash-generating unit level. The recoverable amount of an asset or a cash-generating unit is determined at the higher of its fair value less costs of disposal or its value in use. In determining the value in use, the estimated future cash flows are discounted to their present value using a discount rate that reflects the time value of money and the risks specific to the asset. If the carrying amount of the asset or cash-generating unit exceeds the recoverable amount, impairment loss is recognized in profit or loss and the carrying amount is reduced to the recoverable amount. An asset or a cash-generating unit other than goodwill, for which impairment losses were recognized in prior years, is assessed at the end of the reporting period to determine whether there is any indication that the impairment loss recognized in prior periods may no longer exist or may have decreased. If any such indication exists, the recoverable amount of the asset or cash-generating unit is estimated. In cases the recoverable amount exceeds the carrying amount of the asset or cash-generating unit, the impairment loss is reversed up to the lower of the estimated recoverable amount or the carrying amount, net of depreciation and amortization, that would have been determined if no impairment loss had been recognized in prior years. The reversal of impairment loss is immediately recognized in profit or loss.

Inventories

Inventories are measured at the lower of cost or net realizable value. The cost of inventories is determined mainly using the weighted-average cost formula. The cost of inventories includes purchase costs, costs of conversion, and other costs incurred in bringing the inventories to the present location and condition. Net realizable value is the estimated selling price in the ordinary course of business less the estimated costs of completion and the estimated costs necessary to make the sale. Pre-launch inventory is held as an asset when there is a high probability of regulatory approval for the product. Before that point, a provision is made against the carrying value to its recoverable amount. The provision is then reversed at the point when a high probability of regulatory approval is determined.

Cash and cash equivalents

Cash and cash equivalents consist of cash on hand, demand deposits and short-term, highly liquid investments that are readily convertible to known amounts of cash and subject to insignificant risk of change in value and due within three months from the date of acquisition.

Assets Held for Sale

An asset or disposal group for which the cash flows are expected to arise principally from sale rather than continuing use is classified as an asset held for sale when it is highly probable that the asset or disposal group will be sold within one year, the asset or disposal group is available for immediate sale in its present condition, and the management of Takeda is committed to the sale. In such cases, the asset held for sale is measured at the lower of its carrying amount and fair value less costs to sell.

Property, plant and equipment and intangible assets classified as held for sale are not depreciated or amortized. Assets and liabilities classified as held for sale are presented separately as current items in the consolidated statements of financial position.

Post-employment Benefit

Takeda sponsors lump-sum payments on retirement, pensions and other plans such as post-retirement medical care as post-employment benefit plans. They are classified as defined benefit plans or defined contribution plans, depending on the characteristics of the plans.

Defined Benefit Plans

Takeda uses the projected unit credit method to determine the present value, the related current service cost, and the past service cost by each defined benefit obligation. The discount rate is determined by reference to market yields on high quality corporate bonds at the end of the reporting period. The net defined benefit liabilities (assets) in the consolidated statements of financial position are calculated by deducting the fair value of the plan assets from the present value of the defined benefit obligations. If the defined benefit plan has a surplus, the net defined benefit asset is limited to the present value of any future economic benefits available in the form of refunds from the plan or reductions in future contributions to the plan. Past service cost defined as the change in the present value of the defined benefit obligation resulting from a plan amendment or curtailment is recognized in profit or loss upon occurrence of the plan amendment or curtailment.

Remeasurement of net defined benefit plans is recognized in full in other comprehensive income and transferred to retained earnings in the period in which they are recognized.

Defined Contribution Plans

The costs for defined contribution plans are recognized as expenses when employees render related services.

Provisions

Takeda recognizes rebates and return reserves if Takeda receives consideration from a customer and expects to refund some or all of that consideration to the customer. In addition, provisions are recognized when Takeda has present legal or constructive obligations as a result of past events, it is probable that outflows of resources embodying economic benefits will be required to settle the obligations and reliable estimates can be made of the amount of the obligations. Takeda's provisions consist primarily of rebates and return reserves, as well as provisions for litigation and restructuring.

Financial Instruments

Takeda's financial instruments include financial instruments related to lease contracts, trade and other receivables and payables, liabilities for contingent consideration under business combinations, derivative instruments, and rights and obligations under employee benefit plans, which are dealt with in specific accounting policies.

Financial Assets

Initial Recognition and Measurement

Financial assets are recognized in the consolidated statements of financial position when Takeda becomes a party to the contract of the instruments. Financial assets, except for investments in debt instruments measured at fair value through profit or loss ("FVTPL"), are initially measured at fair value plus transaction costs that are directly attributable to the acquisition.

- Investments in debt instruments measured at amortized cost: Assets such as trade and other receivables that are held within a business model whose objective is to hold financial assets in order to collect contractual cash flows and whose contractual terms give rise on specified dates to cash flows that are solely payments of principal and interest on the principal amount outstanding are measured at amortized cost. Trade receivables are initially recognized at their invoiced amounts, including any related sales taxes less adjustments for deductions such as impairment loss allowance and cash discounts.

- Investments in debt instruments measured at fair value through other comprehensive income ("FVTOCI"): Assets that are held within a business model objective whose objective is achieved by both collecting contractual cash flows and selling financial assets whose contractual terms give rise on specified dates to cash flows that are solely payments of principal and interest on the principal amount outstanding are measured at FVTOCI.

- Investments in debt instruments measured at FVTPL: Assets that do not meet the criteria for amortized cost or FVTOCI are measured at FVTPL.

- Equity instruments measured at FVTOCI: On initial recognition, Takeda makes an irrevocable FVTOCI election (on an instrument-by-instrument basis) to present the subsequent changes in the fair value of equity instruments in other comprehensive income for certain equity instruments held for the long term for strategic purposes. At the reporting date, Takeda designates all of its equity instruments as financial assets measured at FVTOCI.

Subsequent Measurement and Derecognition

Takeda derecognizes a financial asset only when the contractual right to receive the cash flows from the asset expires or when Takeda transfers the financial asset and substantially all the risks and rewards of ownership of the asset to another entity.

- Investments in debt instruments measured at amortized cost: These assets are subsequently measured at amortized cost using the effective interest method. The amortized cost is reduced by impairment losses. Interest income, foreign exchange gains and losses and impairment are recognized in profit or loss. Any gain or loss on derecognition is recognized in profit or loss.
- Investments in debt instruments measured at FVTOCI: These assets are subsequently measured at fair value. Interest income calculated using the effective interest method, foreign exchange gains and losses and impairment are recognized in profit or loss. Other net gains and losses arising from changes in fair value are recognized in other comprehensive income. Upon derecognition of the investments, the gains and losses accumulated in other comprehensive income related to the investment is reclassified to profit or loss.
- Investments in debt instruments measured at FVTPL: These assets are subsequently measured at fair value, and a gain or loss on debt instruments that is subsequently measured at FVTPL is recognized in profit or loss.
- Equity instruments measured at FVTOCI: These assets are subsequently measured at fair value. Dividends are recognized as income in profit or loss unless the dividend clearly represents a recovery of part of the cost of the investment. Other net gains and losses are recognized in other comprehensive income and are never reclassified to profit or loss. Upon derecognition of the investments, the amounts in other comprehensive income related to the investment is reclassified within equity to retained earnings.

Impairment

Loss allowances are established using an Expected Credit Loss ("ECL") model. The provisions are based on a forward-looking ECL, which includes possible default events on the trade receivables over the entire holding period of the trade receivables. Takeda has elected to measure provisions for trade receivables, contract assets and lease receivables at an amount equal to lifetime ECL. Takeda uses a provisions matrix based on historical loss rates adjusted for forward looking information to calculate ECL. These provisions represent the difference between the contractual amount of the trade receivables, the contract assets and the lease receivables in the consolidated statements of financial position and the estimated collectible net amount.

Financial Liabilities

Initial Recognition and Measurement

Financial liabilities are recognized in the consolidated statements of financial position when Takeda becomes a party to the contract of financial instruments. Financial liabilities are classified, at initial recognition, as financial liabilities measured at FVTPL, bonds and loans, or payables.

Financial liabilities, except for those measured at FVTPL, are initially measured at fair value less transaction costs that are directly attributable to the issuance.

Subsequent Measurement

- Financial liabilities measured at FVTPL: Financial liabilities measured at FVTPL are subsequently measured at fair value, and any gains or losses arising on re-measurement are recognized in profit or loss. Financial liabilities measured at FVTPL include derivatives and financial liabilities associated with contingent consideration arrangements.
- Other financial liabilities, including bonds and loans: Other financial liabilities are measured at amortized cost mainly using the effective interest method.

Derecognition

Takeda derecognizes a financial liability only when the obligation specified in the contract is discharged, canceled, or expires. On derecognition of a financial liability, the difference between the carrying amount and the consideration paid or payable is recognized in profit or loss.

Derivatives

Takeda hedges the risks arising mainly from its exposure to fluctuations in foreign currency exchange rates and interest rates using derivatives such as foreign exchange forward contracts, currency options, interest rate swaps, cross currency interest rate swaps and interest rate future. In addition, Takeda hedges the risks arising from its exposure to fluctuations in prices of renewable energy using forward contracts. Takeda does not enter into derivative transactions for trading or speculative purposes. Derivatives are measured at FVTPL unless the derivative contracts are designated as hedging instruments. The gains and losses on derivatives that are not designed as hedging instruments are recognized in profit or loss. The treatment of the change in fair value for derivatives designated as hedging instruments varies based on the type of hedge as described below.

Hedge Accounting

For foreign currency exposure as a result of translation risk, Takeda designates certain non-derivatives, such as foreign currency denominated debt and certain derivatives such as foreign currency forwards, as net investment hedges of foreign operations. For foreign currency exposure due to foreign currency denominated transactions, Takeda designates certain derivatives, such as foreign currency forwards, currency options and cross currency interest rate swaps, as cash flow hedges of forecasted transactions. For interest risk exposure, Takeda designates derivatives such as interest and cross currency interest rate swaps and forward rate agreements, as cash flow hedges of forecasted transactions. Within the designation documentation at inception. Takeda documents the risk management objective, nature of the risk being hedged, and relationship between hedging instruments and hedged risk based on the strategy for undertaking the hedging relationships. At inception and on a quarterly basis, Takeda also assesses whether the hedging instruments are highly effective in offsetting changes in the fair value or the cash flows of the hedged item.

- Cash flow hedges: the effective portion of changes in the fair value of derivatives designated and qualifying as cash flow hedges is recognized in other comprehensive income. The gain or loss relating to the ineffective portion is recognized immediately in profit or loss. The cumulative gain or loss that was previously recognized in other comprehensive income is reclassified to profit or loss in the same period when the cash flows of the hedged items are recognized in profit or loss and in the same line item in the consolidated statements of profit or loss. The currency basis spread and the time value of the foreign currency options are accounted for and presented as hedging cost under other components of equity separately from cash flow hedges.

- Net investment hedges in foreign operations: the gain or loss on hedging instruments in foreign operation is recognized in other comprehensive income. At the time of disposal of the foreign operations, the cumulative gain or loss recognized in other comprehensive income is reclassified to profit or loss.

Hedge accounting is discontinued when the hedging instrument expires or is sold, terminated or exercised, or when the hedge no longer qualifies for hedge accounting.

Transaction costs of financial liabilities

Transaction costs relating to the financial liabilities of debt issued are recorded against the corresponding debt and amortized to the consolidated statements of profit or loss over the period to the earliest redemption date of the debt, using the effective interest rate method. On extinguishment of the related debt, any unamortized deferred transaction costs are written off and charged to interest expense in the consolidated statements of profit or loss.

Share-based Payments

Takeda has implemented share-based payment programs and provides equity and cash-settled share-based payments.

Equity-settled Share-based Payments

Equity-settled share-based payments are granted based on the service performed by the employees, directors, and senior management. The service received and the corresponding increase in equity are measured at the fair value of the equity instruments at the grant date. The fair value of the equity instruments granted to employees, directors, and senior management are recognized as expense over the vesting period of the awards with a corresponding amount as an increase in equity.

Cash-settled Share-based Payments

Cash-settled share-based payments are granted based on the service performed by the employees, directors, and senior management. The service received and the corresponding liability are measured at the fair value of the corresponding liability. The fair value of the liability-classified awards granted to employees, directors, and senior management are recognized as expense over the vesting period of the awards with a corresponding amount as an increase in liability. Takeda re-measures the fair value of the liability at the end of each reporting period and at the date of settlement and recognizes any changes in fair value in profit or loss.

Capital

Ordinary Shares

Proceeds from the issuance of ordinary shares by Takeda are included in share capital and share premium.

Treasury Shares

When Takeda acquires treasury shares, the consideration paid is recognized as a deduction from equity. When Takeda sells the treasury shares, the difference between the carrying amount and the consideration received is recognized in share premium.

4. Operating Segment and Revenue Information

Takeda comprises a single operating segment and is engaged in the research, development, manufacturing, marketing and out-licensing of pharmaceutical products. This is consistent with how the financial information is viewed in allocating resources, measuring performance, and forecasting future periods by the CEO who is Takeda's Chief Operating Decision Maker.

Disaggregation of Revenue Information

Takeda's revenue from contracts with customers is comprised of the following:

Revenue by Type of Good or Service

	JPY (millions) For the Year Ended March 31		
	2021	2022	2023
Sales of pharmaceutical products	¥ 3,105,376	¥ 3,295,723	¥ 3,922,280
Out-licensing and service income	92,436	273,283	105,198
Total	¥ 3,197,812	¥ 3,569,006	¥ 4,027,478

Revenue by Therapeutic Area and Product

	JPY (millions) For the Year Ended March 31		
	2021	2022	2023
Gastroenterology:			
ENTYVIO	¥ 429,281	¥ 521,778	¥ 702,744
TAKECAB/VOCINTI [1]	84,822	102,397	108,719
GATTEX/REVESTIVE	64,564	75,751	93,076
DEXILANT	55,572	50,763	69,371
PANTOLOC/CONTROLOC [2]	43,120	40,275	45,518
ALOFISEL	784	1,843	2,725
Others	99,657	82,877	72,388
Total Gastroenterology	777,800	875,685	1,094,541
Rare Diseases:			
Rare Hematology:			
ADVATE	128,535	118,491	118,188
ADYNOVATE/ADYNOVI	58,070	60,726	66,553
FEIBA	44,495	39,162	41,268
RECOMBINATE	13,389	12,297	12,762
HEMOFIL/IMMUNATE/IMMUNINE	18,662	17,722	19,581
Others	26,648	35,291	46,367
Total Rare Hematology	289,799	283,689	304,718
Rare Genetics and Other:			
TAKHZYRO	86,718	103,242	151,800
ELAPRASE	68,786	73,119	85,321
REPLAGAL	51,764	51,714	66,741
VPRIV	38,518	42,408	48,372
LIVTENCITY	—	1,325	10,501
Others	56,161	55,698	55,989
Total Rare Genetics and Other	301,947	327,507	418,724
Total Rare Diseases	591,746	611,196	723,442

	JPY (millions) For the Year Ended March 31		
	2021	2022	2023
PDT Immunology:			
immunoglobulin	334,874	385,864	522,211
albumin	57,580	90,035	121,446
Others	27,935	31,052	34,786
Total PDT Immunology	420,389	506,951	678,443
Oncology:			
LEUPLIN/ENANTONE	95,365	106,459	111,311
NINLARO	87,396	91,203	92,691
ADCETRIS	59,432	69,190	83,937
ICLUSIG	34,193	34,860	47,206
VELCADE	101,112	110,046	27,759
ALUNBRIG	8,806	13,644	20,556
EXKIVITY	—	962	3,732
Others	30,208	42,367	51,551
Total Oncology	416,512	468,730	438,742
Neuroscience:			
VYVANSE/ELVANSE	271,531	327,052	459,289
TRINTELLIX	68,869	82,315	100,081
Others	76,897	72,926	78,341
Total Neuroscience	417,297	482,294	637,711
Other:			
AZILVA-F [(1)]	82,205	76,297	72,897
LOTRIGA	31,765	32,690	16,732
Others [(3)]	460,098	515,164	364,968
Total Other	574,068	624,150	454,598
Total	¥ 3,197,812	¥ 3,569,006	¥ 4,027,478

(1) The figures include the amounts of fixed dose combinations and blister packs.

(2) Generic name: pantoprazole

(3) The figure for the year ended March 31, 2021 include the revenue of Takeda Consumer Healthcare Company Limited, which was divested on March 31, 2021.
The figure for the year ended March 31, 2022 includes the 133,043 million JPY selling price on sales of four diabetes products (NESINA, LIOVEL, INISYNC and ZAFATEK) in Japan to Teijin Pharma Limited recorded as revenue. As Takeda transferred only the assets, marketing rights and, eventually, marketing authorization associated with the pharmaceutical products which do not entail transfer of employees or associated contracts, Takeda applied IFRS 15 to the transaction and recorded the selling price in revenue.

Geographic Information

Takeda's revenue from contracts with customers is based in the following geographic locations:

	JPY (millions) For the Year Ended March 31		
	2021	2022	2023
Japan	¥ 559,748	¥ 658,983	¥ 512,043
U.S.	1,567,931	1,714,421	2,103,772
Europe and Canada	666,177	739,168	842,668
Asia (excluding Japan)	156,240	196,964	225,007
Latin America	121,638	128,467	160,375
Russia/CIS	57,560	62,057	88,431
Other	68,518	68,945	95,182
Total	¥ 3,197,812	¥ 3,569,006	¥ 4,027,478

"Other" includes the Middle East, Oceania and Africa. This disaggregation provides revenue attributable to countries or regions based on the customer location.

Takeda's non-current assets are held in the following geographic locations:

	JPY (millions) As of March 31	
	2022	2023
Japan	¥ 401,019	¥ 373,133
U.S.	6,663,654	7,560,491
Switzerland	1,514,645	799,325
Ireland	104,943	792,382
Other	1,172,959	1,258,787
Total	¥ 9,857,219	¥ 10,784,117

Non-current assets exclude financial instruments, deferred tax assets and net defined benefit assets.

Information Related to Major Customers

During the years ended March 31, 2021 and 2022, AmerisourceBergen Corporation and its subsidiaries (collectively, "AmerisourceBergen Group") and McKesson Corporation and its subsidiaries (collectively, "McKesson Group") represented more than 10% of Takeda's sales. The sales to AmerisourceBergen Group were 370,759 million JPY and 504,487 million JPY for the years ended March 31, 2021 and 2022, respectively. The sales to McKesson Group were 345,292 million JPY and 406,709 million JPY for the years ended March 31, 2021 and 2022, respectively.

During the year ended March 31, 2023, AmerisourceBergen Group, McKesson Group and Cardinal Health, Inc. and its subsidiaries (collectively, "Cardinal Health Group") represented more than 10% of Takeda's sales. The sales to AmerisourceBergen Group, McKesson Group and Cardinal Health Group were 575,294 million JPY, 540,356 million JPY and 424,527 million JPY, respectively, for the year ended March 31, 2023.

Other Revenue Information

Contract Balances

	JPY (millions) As of March 31	
	2022	2023
Receivables from contracts with customers		
Trade receivables (Note 17)	¥ 617,518	¥ 575,431
Contract assets		
Unbilled receivables	5,926	2,628
Contract liabilities		
Deferred income (Note 24)	50,832	8,609
Advance payments	81	19

Takeda's contract assets relate to the right to receive consideration where performance was completed based on the contract, and trade receivables are recognized when the right to receive consideration becomes unconditional.

Takeda's contract liabilities primarily relate to out-licensing arrangements or product purchase and supply agreements where Takeda receives cash consideration prior to the completion of its performance obligations under the agreements. The revenue recognized during the years ended March 31, 2021, 2022, and 2023 that was included in the contract liability balance as of the beginning of the year was 1,165 million JPY, 30,022 million JPY, and 49,319 million JPY, respectively. The revenue recognized during the years ended March 31, 2021, 2022, and 2023 from performance obligations satisfied (or partially satisfied) in previous periods was 57,903 million JPY, 49,220 million JPY, and 79,251 million JPY, respectively, and primarily relates to royalty income.

Transaction price allocated to the remaining performance obligations

	JPY (millions)			
		Duration of the remaining performance obligations		
	Total	Within one year	Between one and five years	More than five years
Contract liabilities as of March 31, 2022	¥ 50,913	¥ 43,721	¥ 5,288	¥ 1,904
Contract liabilities as of March 31, 2023	8,628	6,394	458	1,775

5. Other Operating Income and Expenses

	JPY (millions) For the Year Ended March 31		
	2021	2022	2023
Other operating income:			
Change in fair value of financial assets and liabilities associated with contingent consideration arrangements (Note 27)	¥ 13,663	¥ 11,195	¥ —
Gain on sales of property, plant and equipment and investment property	4,734	1,148	2,094
Gain on divestment of business to Teva Takeda Yakuhin	1,460	1,414	6,807
Gain on divestment of business and subsidiaries (Note 19)	228,923	5,602	—
Change in estimate of liabilities related to SHP647	60,179	—	4,102
Other	9,061	23,762	12,421
Total	¥ 318,020	¥ 43,123	¥ 25,424
Other operating expenses:			
Donations and contributions	¥ 8,412	¥ 8,255	¥ 7,685
Restructuring expenses (Note 23)	115,875	83,836	59,234
Change in fair value of financial assets and liabilities associated with contingent consideration arrangements (Note 27)	72,940	—	3,991
Valuation reserve for pre-launch inventories	19,486	20,723	9,466
Impairment of assets held for sale (Note 19)	530	—	4,693
Other	41,652	46,261	60,178
Total	¥ 258,895	¥ 159,075	¥ 145,247

For the year ended March 31, 2021, gain on divestment of business and subsidiaries includes sale of shares and relevant assets of Takeda Consumer Healthcare Company Limited and other non-core assets. Change in estimate of liabilities related to SHP647 for the year ended March 31, 2021 is revaluation gain of liabilities for the future costs, such as program termination costs of pipeline compound SHP647 and certain associated rights ("SHP647")(Note). This revaluation gain was recorded upon the European Commission's decision in May 2020 to release Takeda's obligation to divest SHP647.

(Note) Upon the Shire Acquisition in January 2019, the European Commission required Takeda to divest SHP647 and certain associated rights and we recorded a liability associated with that obligation.

For the year ended March 31, 2021, change in fair value of financial assets associated with contingent consideration arrangements included in other operating expenses is driven by changes in assumptions related to the future sales of XIIDRA previously sold to Novartis, including the impact from Novartis' withdrawal of the Marketing Authorisation Application in Europe.

For the year ended March 31, 2022, other in other operating income includes a compensation for damages and settlement proceeds Takeda received of 8,487 million JPY.

For the years ended March 31, 2021, 2022 and 2023 other in other operating expenses includes legal provision for certain legal proceeding of 17,401 million JPY and 20,319 million JPY and 16,455 million JPY, respectively. Other in other operating expenses for the year ended March 31, 2023 also includes a 16,470 million JPY write-off of option fees Takeda paid as part of collaboration agreements.

6. Finance Income and Expenses

	JPY (millions) For the Year Ended March 31		
	2021	2022	2023
Finance Income:			
Interest income			
Interest income from financial assets measured at amortized cost	¥ 1,117	¥ 3,880	¥ 4,187
Interest income from financial assets measured at fair value through P&L	660	700	1,318
Interest income on sublease	4	11	3
Total interest income	1,781	4,591	5,508
Dividend income			
Dividend income from financial assets measured at fair value through OCI and disposed of during the period	252	8	6
Dividend income from financial assets measured at fair value through OCI and held at end of the period	120	164	267
Total dividend income	372	172	273
Gain on derivative financial assets – Foreign exchange hedge	81,744	—	4,476
Gain on derivative financial assets – Warrants	10,246	—	15,896
Gain on derivative financial assets – Virtual power purchase agreement	—	—	6,843
Remeasurement to fair value of pre-existing interest in an acquiree	—	8,482	22,416
Other	11,378	10,455	7,501
Total	¥ 105,521	¥ 23,700	¥ 62,913
Finance Expenses:			
Interest expense			
Interest expense on financial debt	¥ 118,682	¥ 108,498	¥ 100,393
Interest expense on lease liabilities	12,124	13,934	16,580
Total interest expense	130,806	122,432	116,973
Loss on derivative financial assets – Foreign exchange hedge	—	2,112	—
Loss on derivative financial assets – Warrants	—	20,483	—
Loss on derivative financial assets – Virtual power purchase agreement	—	—	6,843
Loss on foreign currency exchange, net	97,319	1,791	14,205
Hyperinflation effect expense	—	3,698	12,256
Other	20,506	16,091	19,421
Total	¥ 248,631	¥ 166,607	¥ 169,698

7. Income Taxes

Income Tax Expense (Benefit)

The composition of income tax expense (benefit) is as follows:

	JPY (millions) For the Year Ended March 31		
	2021	2022	2023
Current tax expense	¥ 131,952	¥ 208,513	¥ 246,578
Deferred tax benefit	(141,888)	(136,108)	(188,526)
Total	¥ (9,936)	¥ 72,405	¥ 58,052

Current tax expense includes the benefits arising from previously unrecognized tax losses, tax credits and temporary differences of prior periods. These effects decreased current tax expense by 12,236 million JPY, 11,315 million JPY and 17,529 million JPY for the years ended March 31, 2021, 2022 and 2023, respectively.

Deferred tax benefit includes the benefits arising from previously unrecognized tax losses, tax credits and temporary differences of prior periods. These effects decreased deferred tax expense by 57,200 million JPY, 11,914 million JPY and 54,974 million JPY for the years ended March 31, 2021, 2022 and 2023, respectively.

Takeda is mainly subject to income taxes, inhabitant tax, and deductible enterprise tax in Japan. The statutory tax rate calculated based on these taxes is 30.6% for the years ended March 31, 2021, 2022 and 2023.

The following is a reconciliation from income tax expense at Takeda's domestic (Japanese) statutory tax rate to Takeda's income tax expense (benefit) reported for the year ended March 31:

	JPY (millions)		
	2021	2022	2023
Profit before tax	¥ 366,235	¥ 302,571	¥ 375,090
Income tax expense at Takeda's domestic (Japanese) statutory tax rate of 30.6%	111,995	92,526	114,703
Non-deductible expenses for tax purposes [(1)]	26,117	6,071	15,158
Changes in unrecognized deferred tax assets and deferred tax liabilities [(2)]	(137,032)	(8,831)	(21,791)
Tax credits	(25,673)	(32,948)	(26,676)
Differences in applicable tax rates of overseas subsidiaries [(3)]	(258)	24,496	(31,446)
Changes in tax effects of undistributed profit of overseas subsidiaries	5,694	(20,359)	6,174
Effect of changes in applicable tax rates and tax law [(4)]	(5,073)	(39,661)	2,482
Tax contingencies [(5)]	(13,164)	58,540	13,991
Effect of prior year items	(10,689)	(4,762)	(7,524)
Entity reorganizations/Divestments [(6)]	36,117	2,041	(6,321)
Other	2,030	(4,708)	(698)
Income tax expense (benefit) reported for the year	¥ (9,936)	¥ 72,405	¥ 58,052

[(1)] Amounts for the years ended March 31, 2021, 2022 and 2023 include the impact from intra territory eliminations, the pre-tax effect of which has been eliminated in arriving at Takeda's consolidated income from continuing operations before income taxes. Amount for the years ended March 31, 2021 and March 31, 2023 also include non-deductible interest due to Japanese earnings stripping rules.

[(2)] Amounts for the years ended March 31, 2021, 2022 and 2023 include deferred tax expenses (benefits) associated with carried forward net operating losses. Amount for the year ended March 31, 2021 is driven by capital losses related to restructuring of subsidiaries. The amount for the year ended March 31, 2023 is driven by recognition of tax benefits from previously unrecognized tax losses as result of internal entity restructuring transactions.

[(3)] Amounts for the years ended March 31, 2021, 2022 and 2023 include unitary and minimum taxes on overseas subsidiaries.

[(4)] Amount for the year ended March 31, 2022 includes 39,106 million JPY deferred tax benefit related to a blended state tax rate change as a result of legal entity restructuring in the US.

[(5)] Tax benefit amount for the year ended March 31, 2021 primarily relates to the tax benefits driven by favorable audit settlements. Tax expense amount for the year ended March 31, 2022 includes 65,942 million JPY from the AbbVie break fee case.

[(6)] 36,117 million JPY impact for the year ended March 31, 2021 primarily relates to the basis difference of divested assets, between accounting which includes goodwill and tax.

The increase in Takeda's income tax expense between the years ended March 31, 2021 and 2022 was primarily due to a tax charge in the year ended March 31, 2022 arising from a tax assessment involving Irish taxation of the break fee Shire received from AbbVie in connection with the terminated offer to acquire Shire made by AbbVie in 2014. Tax expense related to the write down of deferred tax assets from carried forward net operating losses in Japan and lower tax benefits from legal entity reorganizations were partially offset by a reduction of deferred tax liabilities on undistributed profits and a decrease in US blended state tax rates.

The decrease in Takeda's income tax expense between the years ended March 31, 2022 and 2023 was primarily due to increased tax benefits from recognition of deferred tax assets and decreased tax charges for US international tax provisions in the year ended March 31, 2023. Tax expense for the year ended March 31,2022 includes a charge for the AbbVie break fee case partially offset by the benefits from the US state blended tax rate change and reductions of deferred tax liabilities on undistributed earnings.

As a company with worldwide operations, Takeda is subject to several factors that may affect future tax charges, principally the levels and mix of profitability in different jurisdictions, transfer pricing regulations, tax rates imposed and tax regime reforms. In December 2021, the OECD issued model rules for a new global minimum tax framework (Pillar Two). On March 28, 2023, Japan enacted legislation incorporating the model rules established by the OECD that will apply to years beginning on or after April 1, 2024. Takeda will be required to operate within the global minimum tax framework which requires calculation of a new measure of effective tax rate by jurisdiction. It is possible this may result in top-up taxes in some territories in which Takeda operates. Takeda continues to review the legislation to understand potential impacts.

Deferred Taxes

Deferred tax assets and liabilities reported in the consolidated statements of financial position are as follows:

	JPY (millions) As of March 31	
	2022	2023
Deferred tax assets	¥ 362,539	¥ 366,003
Deferred tax liabilities	(451,511)	(270,620)
Net deferred tax assets (liabilities)	¥ (88,972)	¥ 95,383

The major items and changes in deferred tax assets and liabilities are as follows:

	JPY (millions)				
	As of April 1, 2021	Recognized in profit or (loss)	Recognized in other comprehensive income	Other[(1)]	As of March 31, 2022
Research and development expenses	¥ 35,461	¥ (4,250)	¥ —	¥ 1,988	¥ 33,199
Inventories	90,729	(6,375)	—	10,176	94,530
Property, plant and equipment	(80,344)	9,721	—	848	(69,775)
Intangible assets	(561,950)	131,465	—	(66,995)	(497,480)
Financial assets measured at FVTOCI	(23,766)	—	2,669	14,338	(6,759)
Accrued expenses and provisions	139,239	12,931	—	3,160	155,330
Defined benefit plans	19,270	(468)	(6,107)	761	13,456
Deferred income	20,970	(4,256)	—	(5,489)	11,225
Unused tax losses	150,951	(35,160)	—	3,662	119,453
Tax credits	62,389	(28,573)	—	5,096	38,912
Investments in subsidiaries and associates	(69,151)	37,941	—	—	(31,210)
Cash flow hedges	30,023	—	(957)	(35)	29,031
Other	(2,904)	23,132	(1,411)	2,300	21,116
Total	¥ (189,083)	¥ 136,108	¥ (5,806)	¥ (30,190)	¥ (88,972)

	JPY (millions)				
	As of April 1, 2022	Recognized in profit or (loss)	Recognized in other comprehensive income	Other[(1)]	As of March 31, 2023
Research and development expenses	¥ 33,199	¥ 98,057	¥ —	¥ 4,974	¥ 136,230
Inventories	94,530	11,863	—	4,518	110,911
Property, plant and equipment	(69,775)	2,834	—	(4,818)	(71,759)
Intangible assets	(497,480)	86,244	—	(41,358)	(452,594)
Financial assets measured at FVTOCI	(6,759)	—	214	1,417	(5,128)
Accrued expenses and provisions	155,330	(6,402)	—	16,115	165,043
Defined benefit plans	13,456	(2,855)	(5,563)	1,368	6,406
Deferred income	11,225	(3,911)	—	118	7,432
Unused tax losses	119,453	(24,662)	—	6,301	101,092
Tax credits	38,912	9,389	—	3,790	52,091
Investments in subsidiaries and associates	(31,210)	(5,581)	—	(47)	(36,838)
Cash flow hedges	29,031	—	9,449	—	38,480
Other	21,116	23,550	7,485	(8,134)	44,017
Total	¥ (88,972)	¥ 188,526	¥ 11,585	¥ (15,756)	¥ 95,383

[(1)] Other consists primarily of foreign currency translation differences, reclassification of deferred tax assets and liabilities classified as held for sale and the tax impact of items charged directly to equity. The aggregate amount of deferred tax related to items charged directly to equity for the years ended March 31, 2022 and 2023 was (1,460) million JPY and 2,204 million JPY, respectively.

Takeda considers the probability that a portion or all of the future deductible temporary differences, unused tax losses, or unused tax credits can be utilized against future taxable profits upon recognition of deferred tax assets. In assessing the recoverability of deferred tax assets, Takeda considers the scheduled reversal of taxable temporary differences, projected future taxable profits, and tax planning strategies.

Based on the level of historical taxable profits and projected future taxable profits during the periods in which the temporary differences become deductible, Takeda has determined that it is not probable a portion of the tax benefits can be utilized.

The unused tax losses, deductible temporary differences, and unused tax credits for which deferred tax assets were not recognized are as follows:

	JPY (millions) As of March 31	
	2022	2023
Unused tax losses	¥ 1,729,843	¥ 1,181,757
Deductible temporary differences	240,860	259,784
Unused tax credits	10,042	11,186

The unused tax losses and unused tax credits for which deferred tax assets were not recognized will expire as follows:

	JPY (millions) As of March 31	
Unused tax losses	2022	2023
1st year	¥ 131	¥ 76
2nd year	23,670	762
3rd year	1,280	307
4th year	425,654	896
5th year	35,089	2,081
After 5th year	1,184,092	1,114,021
Indefinite	59,927	63,614
Total	¥ 1,729,843	¥ 1,181,757

Unused tax credits	JPY (millions) As of March 31 2022	2023
Less than 5 years	¥ 950	¥ 2,151
5 years or more	9,092	9,034
Indefinite	—	—
Total	¥ 10,042	¥ 11,186

The aggregate amounts of temporary differences associated with investments in subsidiaries for which deferred tax assets were not recognized were 1,184,478 million JPY and 515,052 million JPY as of March 31, 2022 and 2023, respectively.

The aggregate amounts of temporary differences associated with investments in subsidiaries for which deferred tax liabilities were not recognized were 290,208 million JPY and 416,417 million JPY as of March 31, 2022 and 2023, respectively.

Changes in the amounts of unrecognized deferred tax assets and liabilities associated with investments in subsidiaries are primarily due to changes in temporary differences that had no impact on the consolidated statements of profit and loss.

8. Earnings per Share

The basis for calculating basic and diluted earnings per share ("EPS") (attributable to owners of the Company) is as follows:

	For the Year Ended March 31 2021	2022	2023
Net profit for the year attributable to owners of the Company:			
Net profit for the year attributable to owners of the Company JPY (millions)	¥ 376,005	¥ 230,059	¥ 317,017
Net profit used for calculation of earnings per share JPY (millions)	376,005	230,059	317,017
Weighted-average number of ordinary shares outstanding during the year (thousands of shares) [basic]	1,562,006	1,563,501	1,551,809
Dilutive effect (thousands of shares)	11,531	13,668	18,064
Weighted-average number of ordinary shares outstanding during the year (thousands of shares) [diluted]	1,573,537	1,577,169	1,569,872
Earnings per share			
Basic (JPY)	240.72	147.14	204.29
Diluted (JPY)	238.96	145.87	201.94

Basic EPS is calculated by dividing the net profit for the year attributable to owners of the Company, with the weighted average number of ordinary shares outstanding during the year. This calculation excludes the average number of treasury shares. Diluted EPS is calculated by dividing the net profit for the year attributable to owners of the Company, with the weighted-average number of ordinary shares outstanding during the year plus the weighted-average number of ordinary shares that would be issued upon conversion of all the dilutive ordinary shares into ordinary shares.

There were 814 thousand shares, 2,643 thousand shares, and 814 thousand shares that are anti-dilutive stock options, and therefore not included in the calculation of diluted EPS for the years ended March 31, 2021, 2022, and 2023, respectively.

9. Other Comprehensive Income (Loss)

Amounts arising during the year, reclassification adjustments to profit or loss, and tax effects for each component of other comprehensive income (loss) are as follows:

	JPY (millions) For the Year Ended March 31		
	2021	2022	2023
Items that will not be reclassified to profit or loss:			
Changes in fair value of financial assets measured at fair value through OCI:			
Amounts arising during the year	¥ 79,364	¥ (17,295)	¥ (2,868)
Tax effects	(17,498)	2,669	214
Changes in fair value of financial assets measured at fair value through OCI	¥ 61,866	¥ (14,626)	¥ (2,654)
Remeasurement of defined benefit pension plans:			
Amounts arising during the year	¥ 2,147	¥ 26,890	¥ 23,315
Tax effects	2,719	(6,107)	(5,563)
Remeasurement of defined benefit pension plans	¥ 4,866	¥ 20,783	¥ 17,752
Items that may be reclassified subsequently to profit or loss:			
Exchange differences on translation of foreign operations:			
Amounts arising during the year	¥ 284,350	¥ 558,102	¥ 566,683
Reclassification adjustments to profit or (loss)	(112)	—	—
Before tax effects	284,238	558,102	566,683
Tax effects	25,066	25,867	52,090
Exchange differences on translation of foreign operations	¥ 309,304	¥ 583,969	¥ 618,773
Changes in fair value of financial assets measured at fair value through OCI:			
Amounts arising during the year	¥ —	¥ —	¥ (9,118)
Reclassification adjustments to profit or (loss)	—	—	9,118
Before tax effects	—	—	—
Tax effects	—	—	—
Changes in fair value of financial assets measured at fair value through OCI	¥ —	¥ —	¥ —
Cash flow hedges:			
Amounts arising during the year	¥ (40,833)	¥ 82,780	¥ 56,437
Reclassification adjustments to profit or (loss)	(24,485)	(79,321)	(87,337)
Before tax effects	(65,318)	3,459	(30,900)
Tax effects	19,973	(1,286)	9,449
Cash flow hedges	¥ (45,345)	¥ 2,173	¥ (21,451)
Hedging cost:			
Amounts arising during the year	¥ (9,978)	¥ 6,611	¥ (21,426)
Reclassification adjustments to profit or (loss)	(3,200)	(3,071)	(3,052)
Before tax effects	(13,178)	3,540	(24,478)
Tax effects	4,031	(1,083)	7,485
Hedging cost	¥ (9,147)	¥ 2,457	¥ (16,993)
Share of other comprehensive income of investments accounted for using the equity method:			
Amounts arising during the year	¥ (299)	¥ (497)	¥ (892)
Reclassification adjustments to profit or (loss)	—	—	—
Before tax effects	(299)	(497)	(892)
Tax effects	—	—	—
Share of other comprehensive income of investments accounted for using the equity method	¥ (299)	¥ (497)	¥ (892)
Total other comprehensive income (loss) for the year	¥ 321,245	¥ 594,261	¥ 594,535

10. Property, Plant and Equipment

	JPY (millions)					
Acquisition cost	**Buildings and structures**	**Machinery and vehicles**	**Tools, furniture, and fixtures**	**Land**	**Construction in progress**	**Total**
As of April 1, 2021	¥ 1,133,406	¥ 686,135	¥ 133,829	¥ 95,235	¥ 143,130	¥ 2,191,735
Additions and other increases	46,393	20,183	7,911	50	87,220	161,758
Acquisitions through business combinations	—	79	35	—	—	114
Transfers	30,176	41,341	8,070	—	(79,587)	—
Disposals and other decreases	(2,837)	(15,389)	(21,253)	(1,266)	(1,932)	(42,677)
Deconsolidation	—	(4)	—	—	—	(4)
Foreign currency translation differences	81,440	39,680	7,303	4,635	9,024	142,082
As of March 31, 2022	¥ 1,288,578	¥ 772,024	¥ 135,895	¥ 98,654	¥ 157,856	¥ 2,453,007
Additions and other increases	46,155	25,628	9,025	349	104,059	185,217
Transfers	21,026	37,743	5,962	—	(64,731)	—
Disposals and other decreases	(22,876)	(16,084)	(11,096)	(201)	(574)	(50,830)
Reclassification to assets held for sale (Note 19)	(14,915)	(10,968)	(4,013)	(5,471)	(965)	(36,331)
Foreign currency translation differences	82,139	43,039	6,093	4,895	11,755	147,922
As of March 31, 2023	¥ 1,400,108	¥ 851,382	¥ 141,867	¥ 98,227	¥ 207,400	¥ 2,698,984
Accumulated depreciation and accumulated impairment losses						
As of April 1, 2021	¥ (266,705)	¥ (374,845)	¥ (92,866)	¥ (431)	¥ (2,971)	¥ (737,818)
Depreciation expenses	(62,870)	(54,191)	(15,358)	—	—	(132,419)
Impairment losses	—	(346)	(42)	—	—	(388)
Disposals and other decreases	1,353	13,729	21,154	33	76	36,344
Deconsolidation	—	3	—	—	—	3
Foreign currency translation differences	(15,901)	(15,635)	(4,379)	(13)	(1)	(35,929)
As of March 31, 2022	¥ (344,123)	¥ (431,287)	¥ (91,491)	¥ (411)	¥ (2,896)	¥ (870,207)
Depreciation expenses	(72,900)	(60,428)	(17,052)	—	—	(150,379)
Impairment losses	(560)	(1,410)	(121)	—	(239)	(2,331)
Disposals and other decreases	5,429	14,207	10,393	195	—	30,224
Reclassification to assets held for sale (Note 19)	8,209	9,276	3,499	—	—	20,983
Foreign currency translation differences	(15,585)	(16,976)	(3,435)	(28)	(21)	(36,045)
As of March 31, 2023	¥ (419,530)	¥ (486,618)	¥ (98,207)	¥ (243)	¥ (3,156)	¥ (1,007,755)

	JPY (millions)					
Carrying amount	**Buildings and structures**	**Machinery and vehicles**	**Tools, furniture, and fixtures**	**Land**	**Construction in progress**	**Total**
As of April 1, 2021	¥ 866,701	¥ 311,290	¥ 40,963	¥ 94,804	¥ 140,159	¥ 1,453,917
As of March 31, 2022	944,455	340,737	44,404	98,243	154,960	1,582,800
As of March 31, 2023	980,578	364,763	43,660	97,983	204,245	1,691,229

Leases

The changes in acquisition cost of property, plant and equipment for the years ended March 31, 2022 and 2023 include the following changes in ROU assets:

	JPY (millions)			
Acquisition cost of ROU Assets	**Buildings and structures**	**Machinery and vehicles**	**Tools, furniture, and fixtures**	**Total**
As of April 1, 2021	¥ 462,797	¥ 15,040	¥ 472	¥ 478,309
Additions and other increases	30,110	4,195	13	34,318
Disposals and other decreases	(7,365)	(6,177)	(161)	(13,703)
Foreign currency translation differences	39,575	883	27	40,485
As of March 31, 2022	¥ 525,118	¥ 13,940	¥ 351	¥ 539,410
Additions and other increases	31,585	6,828	2	38,416
Disposals and other decreases	(21,134)	(4,842)	(40)	(26,016)
Foreign currency translation differences	38,016	892	7	38,915
As of March 31, 2023	¥ 573,585	¥ 16,818	¥ 320	¥ 590,724

The changes in accumulated depreciation and accumulated impairment losses for the years ended March 31, 2022 and 2023 include the following changes in accumulated depreciation and accumulated impairment loss related to ROU assets:

	JPY (millions)			
Accumulated depreciation and accumulated impairment losses of ROU Assets	**Buildings and structures**	**Machinery and vehicles**	**Tools, furniture, and fixtures**	**Total**
As of April 1, 2021	¥ (82,993)	¥ (8,233)	¥ (303)	¥ (91,529)
Depreciation expenses	(37,820)	(3,867)	(74)	(41,761)
Disposals and other decreases	6,026	5,590	155	11,770
Foreign currency translation differences	(9,380)	(562)	(11)	(9,953)
As of March 31, 2022	¥ (124,166)	¥ (7,072)	¥ (234)	¥ (131,472)
Depreciation expenses	(43,260)	(4,535)	(60)	(47,856)
Impairment losses	(43)	—	—	(43)
Disposals and other decreases	4,039	3,999	39	8,077
Foreign currency translation differences	(8,719)	(429)	(9)	(9,157)
As of March 31, 2023	¥ (172,149)	¥ (8,037)	¥ (264)	¥ (180,450)

The carrying amount of property, plant and equipment includes the carrying amount of following ROU assets:

	JPY (millions)			
Carrying amount of ROU Assets	**Buildings and structures**	**Machinery and vehicles**	**Tools, furniture, and fixtures**	**Total**
As of April 1, 2021	¥ 379,804	¥ 6,807	¥ 169	¥ 386,780
As of March 31, 2022	400,952	6,868	118	407,938
As of March 31, 2023	401,437	8,781	56	410,274

Takeda recognized expenses related to leases not included in the measurement of the lease liabilities as follows:

	JPY (millions) For the Year Ended March 31		
	2021	2022	2023
Expense relating to short-term leases	¥ 4,802	¥ 4,458	¥ 4,521
Expense relating to leases of low-value assets that are not short-term leases expenses	1,250	1,304	1,255
Expense relating to variable lease payments	6,315	4,006	4,794
Total expenses not included in lease liabilities	¥ 12,367	¥ 9,768	¥ 10,570

The total cash outflow for leases for the years ended March 31, 2021, 2022 and 2023 was 51,394 million JPY, 53,628 million JPY and 59,981 million JPY, respectively. Also, the total future cash flow for leases not yet commenced to which Takeda is committed for the year ended March 31, 2023 is 198,293 million JPY.

Impairment

Takeda recognized the following impairment losses, which are reflected as follows, in the consolidated statements of profit or loss:

	JPY (millions) For the Year Ended March 31		
	2021	2022	2023
Cost of sales	¥ (139)	¥ (261)	¥ (375)
Selling, general and administrative expenses	(149)	(34)	(75)
Research and development expenses	(68)	—	—
Other operating expenses	(80)	(92)	(1,881)
Total	¥ (436)	¥ (388)	¥ (2,331)

Impairment losses for the year ended March 31, 2021 resulted primarily from facilities for administrative and sales activities in Japan that were disposed in the year ended March 31, 2021.

Impairment losses for the year ended March 31, 2022 resulted primarily from discontinued production facilities in Japan.

Impairment losses for the year ended March 31, 2023 resulted primarily from a decision to discontinue a production facility in Europe.

The carrying amounts of the impaired assets were reduced to the recoverable amounts, which were measured at fair value less costs of disposal. Fair value less costs of disposal was measured by the sale price indicated on the anticipated sale of the facility or similar transaction less costs of disposal such as property sale commission fee. This fair value is classified as Level 3 in the fair value hierarchy.

11. Goodwill

	JPY (millions) For the Year Ended March 31	
	2022	2023
Acquisition cost		
As of beginning of the year	¥ 4,033,917	¥ 4,407,749
Acquisitions	35,159	—
Reclassification to assets held for sale (Note 19)	—	(5,951)
Foreign currency translation differences and others	338,673	388,925
As of end of the year	¥ 4,407,749	¥ 4,790,723
Carrying amount		
As of beginning of the year	¥ 4,033,917	¥ 4,407,749
As of end of the year	4,407,749	4,790,723

Impairment Testing of Goodwill

For the years ended March 31, 2022 and 2023, respectively, goodwill was tested for impairment at the single operating segment level (one CGU), which is the level at which goodwill is monitored for internal management purposes. Impairment loss for goodwill is recognized if the recoverable amount of goodwill is less than the carrying amount. The recoverable amount is the greater of fair value less costs of disposal, or value in use of the CGU.

For the years ended March 31, 2022 and 2023, respectively, Takeda did not record an impairment loss for goodwill as a result of the impairment testing performed as of January 1. Takeda's market capitalization was compared to the book value of Takeda's net assets and indicated a surplus as of January 1, 2023.

For the years ended March 31, 2022 and 2023, the recoverable amount of goodwill was assessed based on fair value less costs of disposal. The fair value less costs of disposal was determined by discounting the estimated future cash flows based on a 10-year projection using a terminal growth rate and a discount rate as well as deducting the estimated costs of disposal. The projection included the sales forecast related to certain products as the significant assumption, associated with product launches, competition from rival products and pricing policy as well as the possibility of generics entering the market and loss of exclusivity. In setting the sales forecast, Takeda considered past experience, external sources of information, knowledge of competitor activity, and industry trends. The valuation methodology uses significant inputs which are not based on observable market data. Therefore, this fair value less costs of disposal is classified as level 3 in the fair value hierarchy.

Terminal growth rate and discount rate used in the discounted cash flow models for the impairment tests are as follows:

	For the Year Ended March 31	
	2022	2023
Terminal growth rate	0.0%	0.0%
Discount rate (post-tax)	6.2%	6.8%

Terminal growth rate is based on management's estimate of future long-term average growth rates. Discount rate is based on weighted average cost of capital ("WACC") of Takeda.

The fair value less costs of disposal exceeded the carrying amount of the CGU, and a reasonable change in the assumptions used for the recoverable amount calculation would not result in an impairment.

12. Intangible Assets

	JPY (millions)			
Acquisition cost	**Software**	**Intangible assets associated with products**	**Other**	**Total**
As of April 1, 2021	¥ 198,865	¥ 5,706,035	¥ 11,586	¥ 5,916,486
Additions and other increases	33,210	44,944	10	78,164
Acquisitions through business combinations	—	43,682	—	43,682
Disposals and other decreases	(62,078)	(80,911)	(48)	(143,037)
Deconsolidation	(604)	(2)	—	(606)
Foreign currency translation differences	13,385	527,070	6	540,461
As of March 31, 2022	¥ 182,778	¥ 6,240,818	¥ 11,554	¥ 6,435,150
Additions and other increases	36,984	676,156	295	713,436
Disposals and other decreases	(11,798)	(126,610)	(13)	(138,420)
Reclassification to assets held for sale (Note 19)	(1,012)	—	—	(1,012)
Foreign currency translation differences	12,607	533,707	3	546,317
As of March 31, 2023	¥ 219,559	¥ 7,324,072	¥ 11,839	¥ 7,555,471
Accumulated amortization and accumulated impairment losses				
As of April 1, 2021	¥ (103,394)	¥ (1,903,551)	¥ (435)	¥ (2,007,380)
Amortization	(28,560)	(418,788)	(43)	(447,391)
Impairment losses	—	(67,721)	—	(67,721)
Reversal of impairment losses	—	13,595	—	13,595
Disposals and other decreases	61,393	43,635	16	105,044
Deconsolidation	604	—	—	604
Foreign currency translation differences	(6,677)	(206,631)	(49)	(213,357)
As of March 31, 2022	¥ (76,634)	¥ (2,539,461)	¥ (510)	¥ (2,616,606)
Amortization	(25,561)	(485,465)	(30)	(511,056)
Impairment losses	—	(57,341)	—	(57,341)
Disposals and other decreases	10,756	101,888	—	112,643
Reclassification to assets held for sale (Note 19)	397	—	—	397
Foreign currency translation differences	(5,177)	(208,672)	(2)	(213,851)
As of March 31, 2023	¥ (96,220)	¥ (3,189,051)	¥ (542)	¥ (3,285,813)
Carrying amount				
As of April 1, 2021	95,471	3,802,484	11,151	3,909,106
As of March 31, 2022	106,143	3,701,357	11,044	3,818,544
As of March 31, 2023	123,340	4,135,020	11,297	4,269,657

There were no material internally generated intangible assets recorded in the consolidated statements of financial position.

The intangible assets associated with products are comprised of the following:

	JPY (millions)		
	Marketed products	In-process R&D	Carrying amount
As of April 1, 2021	3,427,527	374,957	3,802,484
As of March 31, 2022	3,389,453	311,904	3,701,357
As of March 31, 2023	3,164,380	970,640	4,135,020

Marketed products mainly represent license rights associated with commercialized products. In-process R&D mainly represents products in development and license rights obtained in connection with Takeda's in-licensing and collaboration agreements. These agreements relate to the right to sell products that are being developed (Note 13).

The table below provides information about significant intangible assets.

		JPY (millions) Carrying amount As of March 31		Remaining amortization period As of March 31
		2022	2023	2023
immunoglobulin	Marketed products	¥ 768,871	¥ 766,459	12 Years
TAKHZYRO	Marketed products	546,555	546,336	11 Years
TAK-279	In-process R&D	—	533,999	—
VYVANSE	Marketed products	382,777	306,242	3 Years
ADVATE & ADYNOVATE	Marketed products	293,969	278,463	7 Years
ALUNBRIG	Marketed products	219,943	213,706	8 Years

Impairment

Takeda's impairment assessment for intangible assets requires a number of significant judgments to be made by management to estimate the recoverable amount, including the estimated pricing and costs, likelihood of regulatory approval, and the estimated market and Takeda's share of the market. The most significant assumption for intangible assets associated with marketed products is the product market share of the therapeutic area and estimated pricing, whereas the most significant assumption with pre-marketed products and in-process R&D is the probability of regulatory approval. A change in these assumptions may have a significant impact on the amount, if any, of an impairment charge recorded during a period. For example, negative results from a clinical trial may change the assumption and result in an impairment. Products in development may be fully impaired when a trial is unsuccessful and there is no alternative use for the development asset.

During the year ended March 31, 2021, Takeda recorded impairment losses of 16,635 million JPY. The recoverable amount of the combined impaired assets amounted to 18,255 million JPY. The impairment losses include the loss which resulted from the decision to terminate Takeda's interest in development of an oncology product.

During the year ended March 31, 2022, Takeda recorded impairment losses of 67,721 million JPY. The recoverable amount of the combined impaired assets amounted to 38,951 million JPY. The impairment losses primarily resulted from a decision to terminate development of a GI product and deterioration of the sales forecast for a rare diseases product. This was offset by a reversal of previously recorded impairment losses of 13,595 million JPY mainly related to a rare diseases product which Takeda made a decision to divest. The recoverable amount of the assets related to the reversal was 22,415 million JPY.

During the year ended March 31, 2023, Takeda recorded impairment losses of 57,341 million JPY, primarily resulted from a decision to terminate development of GI products, a decision to terminate a collaboration agreement of an oncology product, and a decision to discontinue manufacturing of a rare diseases product. The recoverable amount of the combined impaired assets amounted to 20,545 million JPY.

These losses are recognized in amortization and impairment losses on intangible assets associated with products in the consolidated statements of profit or loss.

Impairment losses were calculated by deducting the recoverable amount from the carrying amount. The significant assumptions used to calculate the recoverable amount (value in use) are as follows:

	Discount rate (Post-tax)	Discount rate (Pre-tax)
For the year ended March 31, 2021	7.0%	9.2%
For the year ended March 31, 2022	6.5% - 14.0%	8.3% - 17.5%
For the year ended March 31, 2023	6.5% - 22.0%	8.6% - 27.5%

For the year ended March 31, 2022, and 2023, a part of the recoverable amount was measured at fair value less costs of disposal (the amount that was expected to be received by selling the assets). This fair value is classified as Level 3 in the fair value hierarchy.

13. Collaborations, Licensing Arrangements, and Other Asset Acquisitions

Takeda is a party to certain collaborations, in-licensing agreements, out-licensing arrangements and other asset acquisitions.

Out-licensing agreements

Takeda has entered into various licensing arrangements where it has licensed certain products or intellectual property rights for consideration such as up-front payments, equity interest of partners, development milestones, sales milestones and/or sales-based royalty payments. The receipt of the variable considerations related to these substantive milestones is uncertain and contingent on the achievement of certain development milestones or the achievement of a specified level of annual net sales by the licensee.

The following is a description of Takeda's significant out-licensing agreement which Takeda entered into for the past 3 fiscal years.

Neurocrine Biosciences, Inc. ("Neurocrine Biosciences")

In June 2020, Takeda entered into a strategic collaboration with Neurocrine Biosciences to develop and commercialize compounds in Takeda's early-to-mid-stage neuroscience pipeline, including TAK-041, TAK-653 and TAK-831. Takeda received an upfront cash payment in July 2020 and is entitled to certain development milestones, commercial milestones and royalties on net sales. At certain development events, Takeda may elect to opt in or out of a 50:50 profit share on all clinical programs on an asset-by-asset basis. For any asset in which Takeda is participating in a 50:50 profit share arrangement, Takeda will not be eligible to receive development or commercial milestones.

Collaborations, in-licensing arrangements, and other asset acquisitions

These agreements generally provide for commercialization rights to a product or products being developed by the partner, and in exchange, often resulted in an up-front payment being paid upon execution of the agreement and resulted in an obligation that may require Takeda to make future development, regulatory approval, or commercial milestone payments as well as sales-based royalty payments. In some of these arrangements, Takeda and the licensee are both actively involved in the development and commercialization of the licensed products and have exposure to risks and rewards that are dependent on its commercial success. Other asset acquisitions include acquisitions of legal entities that do not qualify as business combinations under IFRS3, such as acquisitions of entities where the value of these acquired entities largely consists of the rights to a single product or group of products.

Under the terms of these collaborations, in-licensing arrangements, and other asset acquisitions, Takeda made the following payments during the years ended March 31:

	JPY (millions)		
	2021	2022	2023
Initial up-front payments, milestone payments, and other asset acquisitions	¥ 84,034	¥ 44,944	¥ 676,156
Acquisition of shares of collaboration and in-licensing partners	1,504	785	494

The following is a description of Takeda's significant collaborations, and in-licensing agreements, and other asset acquisitions which Takeda entered into for the past 3 fiscal years.

Arrowhead Pharmaceuticals Inc. ("Arrowhead")

In October 2020, Takeda entered into a collaboration and licensing agreement with Arrowhead to develop ARO-AAT, a Phase 2 investigational RNA interference (RNAi) therapy in development to treat alpha-1 antitrypsin-associated liver disease (AATLD). ARO-AAT is a potential first-in-class therapy designed to reduce the production of mutant alpha-1 antitrypsin protein, the cause of AATLD progression. Under the terms of the agreement, Takeda and Arrowhead will co-develop ARO-AAT which, if approved, will be co-commercialized in the United States under a 50/50 profit-sharing structure. Outside the U.S., Takeda will lead the global commercialization strategy and receive an exclusive license to commercialize ARO-AAT

with Arrowhead eligible to receive tiered royalties on net sales if approved and commercialized. Arrowhead received an upfront payment and is eligible to receive potential development, regulatory and commercial milestones.

Ovid Therapeutics Inc. ("Ovid")

In March 2021, Takeda secured global rights from Ovid to develop and commercialize the investigational medicine Soticlestat (TAK-935/OV935) for the treatment of developmental and epileptic encephalopathies, including Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS). Original 2017 collaboration between Ovid and Takeda concluded, and Takeda takes the sole responsibility for global development and commercialization. Ovid received an upfront at closing and is also eligible to receive additional development, regulatory and sales milestones and tiered royalties on sales of Soticlestat, if approved and commercialized.

Nimbus Therapeutics, LLC ("Nimbus")

In December 2022, Takeda entered into an agreement to acquire all shares of Nimbus Lakshmi, Inc., a wholly-owned subsidiary of Nimbus. The transaction closed in February 2023. Through this transaction, Takeda acquired TAK-279, formally known as NDI-034858, an oral, selective allosteric tyrosine kinase 2 (TYK2) inhibitor being evaluated for the treatment of multiple autoimmune diseases following successful recent Phase 2b results in psoriasis. Under the terms of the agreement, Takeda agreed to pay 4.0 billion USD upfront following the closing of the transaction*, and will pay two milestone payments of 1.0 billion USD each upon achieving annual net sales of 4.0 billion USD and 5.0 billion USD of products developed from the TAK-279 program.

In addition, in connection with the transaction, Takeda agreed to assume Nimbus's obligations under a January 2022 settlement agreement with Bristol-Myers Squib and its Celgene Corporation subsidiary (collectively, "BMS") to make certain payments to BMS following the achievement of development, regulatory, and sales-based milestones for products developed from the TAK-279 program.

* Of the 4.0 billion USD upfront payment, 3.0 billion USD was paid in February 2023 and 0.9 billion USD was paid in April 2023. Remaining 0.1 billion USD is scheduled to be paid in August 2023.

HUTCHMED (China) Limited and its subsidiary HUTCHMED Limited (collectively, "HUTCHMED")

In January 2023, Takeda entered into an exclusive licensing agreement with HUTCHMED, for the further development and commercialization of fruquintinib outside of mainland China, Hong Kong and Macau. Approved in China in 2018 , fruquintinib is a highly selective and potent inhibitor of vascular endothelial growth factor receptors (VEGFR) -1, 2 and 3. Fruquintinib is orally administered and has the potential to be used across subtypes of refractory metastatic colorectal cancer (CRC), regardless of biomarker status. Under the terms of the agreement, Takeda received an exclusive worldwide license to develop and commercialize fruquintinib in all indications and territories outside of mainland China, Hong Kong and Macau. The transaction closed in March 2023. Subject to the terms of the agreement, Takeda paid HUTCHMED $400 million upfront in April 2023, and will pay up to $730 million in additional potential payments relating to regulatory, development and commercial sales milestones, as well as royalties on net sales.

14. Investments Accounted for Using the Equity Method

Financial information for associates accounted for using the equity method is as follows:
These amounts are based on the ownership interests of Takeda.

	JPY (millions) For the Year Ended March 31		
	2021	2022	2023
Net profit (loss) for the year	¥ 76	¥ (15,367)	¥ (8,630)
Other comprehensive income (loss)	(299)	(497)	(892)
Total comprehensive income (loss) for the year	¥ (223)	¥ (15,863)	¥ (9,522)

The carrying amount of the investments in associates accounted for using the equity method is as follows:

	JPY (millions) As of March 31	
	2022	2023
Carrying amount of investments accounted for using the equity method	¥ 96,579	¥ 99,174

15. Other Financial Assets

	JPY (millions) As of March 31	
	2022	2023
Derivative assets	¥ 41,890	¥ 79,654
Investment in convertible notes at fair value through P&L	10,409	11,435
Investment in debt instruments at fair value through P&L	1,052	1,063
Investment in equity instruments at fair value through OCI	148,451	157,731
Financial assets associated with contingent consideration arrangements	26,852	23,806
Other	30,205	26,168
Total	¥ 258,859	¥ 299,857
Non-current	¥ 233,554	¥ 279,683
Current	¥ 25,305	¥ 20,174

As of March 31, 2022 and 2023, equity instruments included 84,188 million JPY and 74,495 million JPY, respectively, of investments in public companies. These are considered Level 1 in the fair value hierarchy as defined in Note 27. The remainder of the equity instruments primarily relates to investments acquired in connection with collaborations and licensing agreements (Note 13) and are considered Level 3 investments in the fair value hierarchy.

As of March 31, 2022 and 2023, financial assets associated with contingent consideration arrangements are assets mainly recognized in relation to the divestiture of XIIDRA (Note 27) and are considered Level 3 investments in the fair value hierarchy.

16. Inventories

	JPY (millions) As of March 31	
	2022	2023
Finished products and merchandise	¥ 224,102	¥ 269,042
Work-in-process	404,087	436,508
Raw materials and supplies	224,977	280,908
Total	¥ 853,167	¥ 986,457

The amount of inventory write-offs recognized was 24,269 million JPY, 25,018 million JPY, and 18,392 million JPY for the years ended March 31, 2021, 2022 and 2023 respectively, and was included in cost of sales.

17. Trade and Other Receivables

	JPY (millions) As of March 31	
	2022	2023
Trade receivables	¥ 710,304	¥ 674,691
Other receivables	79,127	73,999
Impairment loss allowance	(9,390)	(7,356)
Chargebacks and other allowances	(83,396)	(91,904)
Total	¥ 696,644	¥ 649,429

Takeda utilizes programs to sell certain trade and other receivables to a select group of banks on a non-recourse basis. Under these programs, trade and other receivables sold are derecognized when the risks and rewards of ownership have been transferred. These trade and other receivables relate to specific customers determined in advance and are eligible for sale, but which of them will be sold will be determined by both parties on a monthly basis. Therefore, these trade and other receivables are held for both collecting cash from customers as well as selling to banks.

Trade and other receivables due from customers that Takeda has the option to factor are classified as investments in debt instruments measured at FVTOCI since they are held to collect and sell. As of March 31, 2022 and 2023, trade and other receivables measured at FVTOCI were 20,665 million JPY and 71,080 million JPY, respectively.

18. Cash and Cash Equivalents

	JPY (millions) As of March 31	
	2022	2023
Cash and deposits	¥ 389,059	¥ 229,557
Short-term investments	460,637	303,973
Total	¥ 849,695	¥ 533,530

19. Assets and Disposal Groups Held for Sale

Takeda has classified certain assets as held for sale in the consolidated statements of financial position. Non-current assets and disposal groups are transferred to assets held for sale when it is expected that their carrying amounts will be recovered principally through a sale and the sale is considered highly probable. The non-current assets and disposal groups held for sale are held at the lower of carrying amount or fair value less costs to sell.

Gains or losses recognized from measuring the disposal groups classified as held for sale at the lower of their carrying amounts or fair value less costs to sell are recorded as other operating income or expenses.

Disposal Groups Held for Sale

	JPY (millions) As of March 31
	2023
Property, plant and equipment	¥ 9,847
Goodwill	3,347
Intangible assets	402
Inventories	1,200
Deferred tax assets	45
Other assets	395
Total assets	¥ 15,235
Other liabilities	¥ 144
Total liabilities	¥ 144

During the year ended March 31, 2022, Takeda recognized the 5,602 million JPY divestiture gain in other operating income (Note 5) upon the completion of the divestiture of a group of assets and liabilities associated with a portfolio of non-core prescription pharmaceutical assets sold in China. The proceeds from this divestiture comprised the majority of Takeda's proceeds from sales of business (net of cash and cash equivalents divested) in the consolidated statements of cash flows of 28,196 million JPY for the year ended March 31, 2022 and no impairment was recorded for the year ended March 31, 2022 when disposal groups were classified as held for sale.

The disposal groups held for sale consisted of the followings and its fair value are classified as Level 3 in the fair value hierarchy as of March 31, 2023.

- The assets and liabilities such as intangible assets related to Shonan Health Innovation Park in Japan were classified as held for sale during the year ended March 31, 2023, following management decision and signing an agreement to transfer its operation business to iPi Business Preparation Company (iPark Institute Co., Ltd). The transfer of its operation business was completed in April 2023, and the impact from this transfer on the consolidated statements of profit or loss for the year ended March 31, 2023 was not material.
- Takeda entered into an agreement to transfer manufacturing operation of TACHOSIL in Austria and classified the corresponding assets such as goodwill and property, plant and equipment as held for sale.
- The assets such as property, plant and equipment were classified as held for sale following a sales agreement of Center for Learning and Innovation (CLI) in Japan.

Also, during the year ended March 31, 2023, Takeda classified the assets such as property, plant and equipment as held for sale related to an agreement to divest the manufacturing site in Norway and completed the divestiture. The proceeds from this divestiture comprised the majority of Takeda's proceeds from sales of business (net of cash and cash equivalents divested) in the consolidated statements of cash flows of 7,958 million JPY for the year ended March 31, 2023.

Takeda recorded an impairment loss of 4,693 million JPY in other operating expenses (Note 5) during the year ended March 31, 2023 when disposal groups were classified as held for sale.

20. Bonds and Loans

	JPY (millions) As of March 31	
	2022	2023
Bonds	¥ 3,637,355	¥ 3,658,314
Short-term loans	285	256
Long-term loans	707,770	723,772
Total	¥ 4,345,410	¥ 4,382,341
Non-current	¥ 4,141,418	¥ 4,042,741
Current	¥ 203,993	¥ 339,600

The composition of bonds is as follows:

Instrument	Principal amount in contractual currency (millions)	JPY (millions) Carrying amount		Interest rate (%)	Maturity
		As of March 31, 2022	As of March 31, 2023		
Hybrid subordinated bonds	¥ 500,000	498,154	498,876	1.720% per annum through October 6, 2024 and 6 month LIBOR[5] + margin (1.750-2.750%) thereafter	June 2079
2018 EUR Unsecured Senior Notes – variable rate	€ 750	101,912	—	3 month EURIBOR + margin (1.100%)	November 2022 [3]
2018 EUR Unsecured Senior Notes – fixed rate	€ 3,000	405,290	433,611	2.250-3.000%	November 2026 - November 2030
2018 USD Unsecured Senior Notes – fixed rate	$3,250 as of March 31, 2022 $2,250 as of March 31, 2023	395,303	298,842	4.400-5.000%	November 2023 - November 2028 [2]
Unsecured Senior Notes Assumed in Shire Acquisition	$ 4,000	465,958	515,298	2.875-3.200%	September 2023 - September 2026
Unsecured Senior Notes Assumed in Shire Acquisition	$1,520 as of March 31, 2022 $1,301 as of March 31, 2023	185,998	174,239	2022: 3.600-5.250% 2023: 4.000-5.250%	June 2025 - June 2045 [1]
2020 USD Unsecured Senior Notes – fixed rate	$ 7,000	849,391	928,210	2.050-3.375%	March 2030 - July 2060
2020 EUR Unsecured Senior Notes – fixed rate	€ 3,600	485,985	519,808	0.750-2.000%	July 2027 - July 2040
JPY Unsecured Senior Bonds – fixed rate	¥ 250,000	249,364	249,429	0.400%	October 2031
Commercial Paper	¥ 40,000	—	40,000	—	June 2023
Total		¥ 3,637,355	¥ 3,658,314		

The composition of loans is as follows:

Instrument	Principal amount in contractual currency (millions)	JPY (millions) Carrying amount As of March 31, 2022	JPY (millions) Carrying amount As of March 31, 2023	Interest rate (%)	Maturity
Syndicated Loans 2016	¥ 200,000	200,000	200,000	0.200–0.300%	April 2023 - April 2026
Syndicated Loans 2017	¥ 113,500	113,500	113,500	0.350%	April 2027
USD Syndicated Loans 2017	$ 1,500	183,028	199,993	6 month LIBOR[4] + 0.500%	April 2027
Bilateral Loans	¥ 210,000	210,000	210,000	0.190–0.815%	April 2024-March 2029
Other		1,527	534		
Total		¥ 708,055	¥ 724,027		

On April 23, 2022, Takeda redeemed 219 million USD of unsecured U.S. dollar-denominated senior notes issued in June 2015 in advance of their original maturity date of June 23, 2022[1]. Following this, on October 27, 2022, Takeda redeemed 1,000 million USD of unsecured U.S. dollar-denominated senior notes issued in November 2018 in advance of their original maturity date of November 26, 2023[2]. Furthermore, on November 21, 2022, Takeda redeemed 750 million EUR of unsecured floating rate senior notes issued in November 2018 on their maturity date[3]. On March 31, 2023, Takeda repaid 75 billion JPY in bilateral loans falling due and on the same day entered into new bilateral loans of 75 billion JPY maturing on March 30, 2029. Takeda also had short term commercial paper drawings outstanding of 40 billion JPY as of March 31, 2023, noting that there were no commercial paper drawings as of March 31, 2022.

While the transition away from LIBOR as a benchmark rate did not impact the financing rates that were incurred in fiscal year ended March 31, 2023, Takeda did engage with its financing partners in April 2023 to ensure that SOFR will be effective from July 1, 2023 in respect of the 1,500 million USD Syndicated Loans 2017 where 6 months USD LIBOR will be replaced by 6 months Term SOFR + 0.42826% on interest payment dates from October 2023[4]. In respect of the Hybrid subordinated bonds that attract a fixed interest rate until October 6, 2024 and 6 month JPY LIBOR plus margin thereafter, Takeda will engage with its advisors to determine an alternative benchmark to be used instead of 6 month JPY LIBOR if the bonds are not repaid on the bond call date of October 6, 2024[5]. There are no changes in Takeda's risk management strategy arising from the replacement of the benchmark rate.

In September 2019, Takeda reached an agreement on a commitment facility of 700 billion JPY with various Japanese and non-Japanese banks. The commitment facility has a maturity of September 2026 and is available for general business use. There were no drawdowns on the 700 billion JPY commitment facility as of March 31, 2022 and 2023, respectively.

There are long-term financing agreements that contain financial covenants, a key one of which requires Takeda's ratio of consolidated net debt to adjusted EBITDA, as defined in the loan agreements, for the previous twelve-month period to not surpass certain levels as of March 31 and September 30 of each year. Takeda was in compliance with all financial covenants as of March 31, 2022 and 2023, respectively.

In 2017, Takeda entered into USD to JPY cross currency interest rate swap agreements to fix the interest rate for 925 million USD of the floating rate USD Syndicated Loans 2017. In respect of the remaining 575 million USD of the floating rate USD Syndicated Loans 2017, Takeda entered into an interest rate swap agreement to fix the applicable interest rate. Furthermore, in 2020, Takeda entered into USD to JPY cross currency swaps on 1,750 million USD of the fixed rate 2018 USD Unsecured Senior Notes and 4,000 million USD of the fixed rate 2020 USD Unsecured Senior Notes.

21. Other Financial Liabilities

	JPY (millions) As of March 31	
	2022	2023
Derivative liabilities (Note 27)	¥ 36,529	¥ 40,721
Lease liabilities (Note 27)	465,238	479,351
Financial liabilities associated with programs to sell certain receivables	37,093	78,041
Financial liabilities associated with contingent consideration arrangements (Note 27)	5,844	8,139
Other	120,310	113,554
Total	¥ 665,014	¥ 719,806
Non-current	¥ 468,943	¥ 534,269
Current	¥ 196,071	¥ 185,537

"Other" mainly includes deposits related to certain vaccines operations.

22. Employee Benefits

Defined Benefit Plans

The Company and some of its subsidiaries have various defined benefit plans such as lump-sum retirement payments plans and defined benefit pension plans, which define the amount of benefits that an employee will receive on or after retirement, usually based on one or more factors, such as age, years of employment, compensation, classes, and service.

The Company's defined benefit plans are the most significant plans among Takeda's defined benefit obligations and plan assets.

Defined benefit pension plans

Japan

The Company's corporate defined benefit pension plan in Japan is a funded defined benefit pension plan, which is regulated by the Defined-Benefit Corporate Pension Act, one of the Japanese pension laws. Benefits are paid in exchange for services rendered by employees who worked for more than a specified period, typically three years, considering their years of service and the degree of their contribution to the Company.

The Company's pension fund (the "Fund") is an independent entity established in accordance with the Japanese pension laws, and Takeda has an obligation to make contributions. The Director(s) of the Fund has the fiduciary duty to comply with laws; the directives by the Minister of Health, Labour and Welfare, and the Director-Generals of Regional Bureaus of Health and Welfare made pursuant to those laws; and the by-laws of the Fund and the decisions made by the Board of Representatives of the Fund. Contributions are also regularly reviewed and adjusted as necessary to the extent permitted by laws and regulations.

Foreign

Other types of defined benefit pension plans operated by Takeda are generally established and operated in the same manner as described above and in accordance with local laws and regulations where applicable.

The present value of the defined benefit obligation is calculated annually based on actuarial valuations that are dependent upon a number of assumptions, including discount rates and future salary (benefit) increases. Service costs charged to operating expense related to defined benefit plans represent the increase in the defined benefit liability arising from pension benefits earned by active participants in the current period. Takeda is exposed to investment and other experience risks and may need to make additional contributions where it is estimated that the benefits will not be met from regular contributions, expected investment income, and assets held.

The amounts recognized in the consolidated statements of profit or loss and the consolidated statements of financial position are as follows:

Consolidated statements of profit or loss

	JPY (millions) For the Year Ended March 31		
	2021	2022	2023
Japan	¥ (2,696)	¥ 2,992	¥ 2,990
Foreign	10,655	14,387	13,782
Defined benefit costs	¥ 7,959	¥ 17,379	¥ 16,772

Consolidated statements of financial position

	JPY (millions) As of March 31, 2022		
	Japan	Foreign	Total
Present value of defined benefit obligations	¥ 168,449	¥ 254,462	¥ 422,912
Fair value of plan assets	225,363	117,140	342,503
Effect of asset ceiling	30,953	—	30,953
Net defined benefit liabilities (assets)	¥ (25,961)	¥ 137,323	¥ 111,362
Consolidated statements of financial position			
Net defined benefit liabilities	¥ 8,524	¥ 137,323	¥ 145,847
Net defined benefit assets	34,485	—	34,485
Net amount of liabilities (assets) recognized in the consolidated statements of financial position	¥ (25,961)	¥ 137,323	¥ 111,362

	JPY (millions) As of March 31, 2023		
	Japan	Foreign	Total
Present value of defined benefit obligations	¥ 153,371	¥ 247,725	¥ 401,096
Fair value of plan assets	217,296	128,333	345,630
Effect of asset ceiling	41,311	—	41,311
Net defined benefit liabilities (assets)	¥ (22,614)	¥ 119,392	¥ 96,777
Consolidated statements of financial position			
Net defined benefit liabilities	¥ 8,202	¥ 119,392	¥ 127,594
Net defined benefit assets	30,816	—	30,816
Net amount of liabilities (assets) recognized in the consolidated statements of financial position	¥ (22,614)	¥ 119,392	¥ 96,777

Net defined benefit assets were included in other non-current assets on the consolidated statements of financial position.

Defined benefit obligations

A summary of changes in present value of the defined benefit obligations for the periods presented is as follows:

	JPY (millions) For the Year Ended March 31, 2022		
	Japan	Foreign	Total
At beginning of year	¥ 180,321	¥ 251,767	¥ 432,088
Current service cost	3,098	10,934	14,032
Interest cost	1,209	3,545	4,754
Remeasurement of defined benefit pension plans			
From changes in demographic assumptions	97	(2,313)	(2,216)
From changes in financial assumptions	(2,994)	(28,726)	(31,720)
Experience adjustments	(2,522)	4,457	1,935
Past service cost	40	1,400	1,440
Benefits paid	(10,799)	(9,971)	(20,769)
Contributions by the employees	—	2,297	2,297
Effect of business combinations and disposals	—	60	60
Foreign currency translation differences	—	21,013	21,013
At end of the year	¥ 168,449	¥ 254,462	¥ 422,912

	JPY (millions) For the Year Ended March 31, 2023		
	Japan	Foreign	Total
At beginning of year	¥ 168,449	¥ 254,462	¥ 422,912
Current service cost	3,174	10,787	13,961
Interest cost	1,371	5,838	7,209
Remeasurement of defined benefit pension plans			
From changes in demographic assumptions	164	102	266
From changes in financial assumptions	(10,735)	(42,603)	(53,338)
Experience adjustments	459	3,477	3,935
Past service cost	—	(38)	(38)
Benefits paid	(9,511)	(9,955)	(19,467)
Contributions by the employees	—	3,807	3,807
Effect of business combinations and disposals	—	—	—
Foreign currency translation differences	—	21,849	21,849
At end of the year	¥ 153,371	¥ 247,725	¥ 401,096

The remaining weighted average duration of the defined benefit obligations was 14.0 years and 12.6 years as of March 31, 2022 and 2023, respectively.

Significant actuarial assumptions used to determine the present value are as follows:

	Discount rate	Future salary increases
As of March 31, 2022		
Japan	0.8%	2.5%
Foreign	2.1%	2.8%
As of March 31, 2023		
Japan	1.3%	—
Foreign	3.4%	3.0%

Takeda has cash balance plans and the future salary increase is not used to determine the present value of the defined benefit obligations for those plans. As of March 31, 2022, future salary increases were not used to determine the present value of the defined benefit obligations related to certain defined benefit plans in Japan and foreign countries. As of March 31, 2023, future salary increases were not used to determine the present value of the defined benefit obligations related to all the defined benefit plans in Japan and certain plans in foreign countries.

A 0.5% change in these actuarial assumptions would affect the present value of defined benefit obligations at the end of the reporting period, while holding all other assumptions constant, by the amounts shown below:

	JPY (millions)			
	Discount Rate		Future Salary Increases	
	Change in assumption	Impact	Change in assumption	Impact
As of March 31, 2022				
Japan	+0.50 %	(10,756)	+0.50 %	6
	-0.50 %	11,699	-0.50 %	(6)
Foreign	+0.50 %	(16,997)	+0.50 %	3,654
	-0.50 %	19,192	-0.50 %	(3,334)
As of March 31, 2023				
Japan	+0.50 %	(9,235)	+0.50 %	—
	-0.50 %	10,000	-0.50 %	—
Foreign	+0.50 %	(14,411)	+0.50 %	3,578
	-0.50 %	15,931	-0.50 %	(3,278)

Plan assets

The defined benefit plans are independent of Takeda and funded only by contributions from Takeda. Takeda's investment policies are designed to secure the necessary returns in the long-term within acceptable risk levels to ensure payments of pension benefits to eligible participants, including future participants. The acceptable risk level in the return rate on the plan assets is derived from a detailed study considering the mid- to long-term trends and the changes in income such as contributions and payments. Based on policies and studies, after consideration of issues such as the expected rate of return and risks, Takeda formulates a basic asset mix which aims at an optimal portfolio on a long-term basis with the selection of appropriate investment assets.

A summary of changes in fair value of plan assets for the periods presented is as follows:

	JPY (millions) For the Year Ended March 31	
	2022	2023
Balance at beginning of the year	¥ 333,392	¥ 342,503
Interest income on plan assets	3,016	4,608
Remeasurement of defined benefit plans Return on plan assets	(85)	(15,712)
Contributions by the employer	7,581	12,769
Contributions by the employees	2,297	3,807
Benefits paid	(15,084)	(13,589)
Foreign currency translation differences	11,387	11,244
Balance at end of the year	¥ 342,503	¥ 345,630

Takeda expects to contribute 12,485 million JPY to the defined benefit plans for the year ending March 31, 2024.

The breakdown of fair value by asset class is as follows:

	JPY (millions) As of March 31			
	2022		2023	
	With quoted prices in active markets	No quoted prices in active markets	With quoted prices in active markets	No quoted prices in active markets
Equities:				
Japan	¥ 10,156	¥ 2,713	¥ 9,911	¥ 2,178
Foreign	34,924	101,870	38,277	81,265
Bonds:				
Japan	1,296	15,876	14,567	17,405
Foreign	21,028	46,683	10,407	33,893
Life insurance company general accounts	—	72,556	—	70,775
Investment trust funds	—	12	—	40,026
Cash and cash equivalent	10,106	—	7,681	—
Others	(1,069)	26,350	517	18,727
Total plan assets	¥ 76,442	¥ 266,061	¥ 81,360	¥ 264,269

Equities and bonds with no quoted prices in active markets includes pooled funds that are primarily invested in listed securities on active markets. Life insurance company general accounts are accounts with guaranteed capital and minimum interest rate, in which life insurance companies manage funds on a pooled basis.

Changes in effect of asset ceiling for the periods presented are as follows:

	JPY (millions) For the Year Ended March 31	
	2022	2023
Balance at beginning of the year	¥ 25,757	¥ 30,953
Interest income	170	248
Remeasurement Changes in effect of asset ceiling	5,026	10,110
Balance at end of the year	¥ 30,953	¥ 41,311

Defined Contribution Plans

The Company and some of the Company's subsidiaries offer defined contribution benefit plans.

Benefits of defined contribution plans are linked to contributions paid, the performance of each participant's chosen investments, and the form in which participants choose to redeem their benefits. Contributions made into these plans are generally paid into an independently administered fund.

Contributions payable by Takeda for these plans are charged to operating expenses. Takeda has no exposure to investment risks and other experience risks with regard to defined contribution plans.

The amount of defined contribution costs was 34,052 million JPY, 37,345 million JPY, and 46,446 million JPY for the years ended March 31, 2021, 2022, and 2023, respectively. These amounts include contributions to publicly provided plans.

Other Employee Benefit Expenses

Major employee benefit expenses other than retirement benefits for each fiscal year are as follows:

	JPY (millions) For the Year Ended March 31		
	2021	2022	2023
Salary	¥ 418,087	¥ 458,039	¥ 573,080
Bonuses	105,772	127,888	133,792
Other	163,443	187,440	237,857

The above table does not include severance expenses.

23. Provisions

The movements in the provisions are as follows:

	JPY (millions)				
	Litigation (Note 32)	Restructuring	Rebates and return reserves	Other	Total
As of April 1, 2021	¥ 73,395	¥ 32,297	¥ 377,772	¥ 26,562	¥ 510,026
Increases	28,235	12,193	835,096	24,826	900,351
Decreases (utilized)	(59,386)	(16,280)	(833,159)	(15,651)	(924,476)
Decreases (reversed)	(252)	(15,948)	(10,574)	(3,739)	(30,513)
Foreign currency translation differences	877	1,091	35,846	2,498	40,312
As of March 31, 2022	¥ 42,869	¥ 13,353	¥ 404,982	¥ 34,497	¥ 495,701
Increases	25,096	7,807	1,005,330	17,095	1,055,328
Decreases (utilized)	(3,981)	(12,098)	(953,287)	(16,538)	(985,905)
Decreases (reversed)	(95)	(1,066)	(25,624)	(11,200)	(37,985)
Foreign currency translation differences	402	956	33,813	2,019	37,190
As of March 31, 2023	¥ 64,290	¥ 8,951	¥ 465,214	¥ 25,874	¥ 564,329

The current portion of the provision is 471,278 million JPY, 443,502 million JPY, and 508,360 million JPY as of April 1, 2021, March 31, 2022 and 2023, respectively. The non-current portion of the provision is 38,748 million JPY, 52,199 million JPY and 55,969 million JPY, as of April 1, 2021, March 31, 2022 and 2023, respectively.

Restructuring

Takeda has various restructuring efforts in place during the years ended March 31, 2021, 2022 and 2023, in connection with the following:

- Transform its R&D function – Takeda has led various restructuring efforts during the year ended March 31, 2021, in connection with efforts to transform its R&D function and to improve the efficiency of its operations. These initiatives included consolidation of sites and functions and reduction in workforce.
- Integration of Shire - In the years ended March 31, 2021, 2022 and 2023, Takeda directed various restructuring efforts following the Shire acquisition. The integration of Shire includes initiatives to consolidate systems, sites, and functions, and to optimize the workforce.
- Various other efforts to improve the efficiency of its operations and related facilities.

A restructuring provision is recorded when Takeda has developed a detailed formal plan for the restructuring. Takeda records the provision and associated expenses based on estimated costs associated with the plan. The ultimate cost and the timing of any payments under the plan will be impacted by the actual timing of the actions and the actions of employees impacted by the restructuring activities.

Restructuring expenses recorded for the fiscal years ended March 31, 2021, 2022 and 2023 are as follows:

	JPY (millions) For the Year Ended March 31		
	2021	2022	2023
Cash:			
Severance	¥ 28,031	¥ 15,230	¥ 10,605
Consulting fees	5,704	2,963	12,709
Other	70,742	65,163	33,601
Total	¥ 104,477	¥ 83,357	¥ 56,915
Non-Cash:			
Depreciation and impairment	¥ 11,398	¥ 479	¥ 2,320
Total	¥ 115,875	¥ 83,836	¥ 59,234

Other restructuring expenses for the fiscal years ended March 31, 2021, 2022 and 2023 include personnel expenses of 8,091 million JPY, 9,420 million JPY, and 9,683 million JPY, respectively, and mainly related to retention bonus and salary of employees fully dedicated to restructuring programs. Other restructuring expenses for the fiscal year ended March 31, 2021, 2022 and 2023 also include expenses related to system optimization by the integration of Shire in digital transformation initiatives.

Rebates and Returns

Takeda has recognized a provision related mainly to sales rebates and returns for products and merchandises. The balances stated in the summary table above include provisions of 266,113 million JPY and 293,385 million JPY as of March 31, 2022 and 2023, respectively, for contractual and statutory rebates payable under Commercial healthcare provider contracts and U.S. State and Federal government health programs, such as U.S. Medicaid and U.S. commercial managed care programs. These are expected to be paid out generally within one year. Return reserves are recorded primarily for credits expected to be issued to customers for certain expired product that will be returned. Sales rebates and sales returns reserves are reviewed and updated monthly or when there is a significant change in its amount.

Other

Other provisions are primarily related to asset retirement obligations, contract termination fees and onerous contracts.

24. Other Liabilities

	JPY (millions) As of March 31	
	2022	2023
Accrued expenses	¥ 505,466	¥ 531,891
Deferred income	74,551	32,103
Other	72,146	68,083
Total	¥ 652,163	¥ 632,078
Non-current	¥ 67,214	¥ 65,389
Current	¥ 584,949	¥ 566,689

Accrued expenses include accrued employee benefit expenses of 209,772 million JPY and 229,130 million JPY as of March 31, 2022 and 2023, respectively.

Deferred income includes contract liabilities related to out-licensing agreements, product procurement and supply agreements, and government grants for the purchase of property, plant and equipment. The grants received were 15,221 million JPY and 15,894 million JPY during the years ended March 31, 2022 and 2023, respectively. The primary government grants relate to funding a portion of Takeda's investment in the development and production of vaccines. Takeda was reimbursed for investments it made in facilities. The grant income is recognized over the life of the associated assets and is recorded as an offset to the depreciation expense included in cost of sales, selling, general and administrative expenses, and research and development expenses.

25. Trade and Other Payables

	JPY (millions) As of March 31	
	2022	2023
Trade payables	¥ 295,934	¥ 307,453
Other payables	220,364	341,780
Total	¥ 516,297	¥ 649,233

26. Equity and Other Equity Items

	Thousands of Shares For the Year Ended March 31	
	2022	2023
Authorized shares as of the beginning of the year	3,500,000	3,500,000
Shares issued:		
At the beginning of the year	1,576,388	1,582,253
Exercise of stock options	10	44
Issuance of shares	5,855	—
As of the end of the year	1,582,253	1,582,296

The shares issued by the Company are ordinary shares with no par value that have no restrictions on any rights. The number of treasury shares included in the above shares issued was 13,030 thousand shares, 31,892 thousand shares, and 27,767 thousand shares as of April 1, 2021, March 31, 2022, and 2023, respectively. The number of treasury shares as of April 1, 2021, March 31, 2022 and 2023 includes 12,772 thousand shares, 9,161 thousand shares and 6,215 thousand shares, respectively, held by the Employee Stock Ownership Plan ("ESOP") Trust and the Board Incentive Plan ("BIP") Trust. During the year ended March 31, 2022, the ESOP and BIP Trust acquired 1,185 thousand shares and sold 4,796 thousand shares. During the year ended March 31, 2023, the ESOP and BIP Trust acquired 554 thousand shares and sold 3,500 thousand shares.

During the year ended March 31, 2022, the Company issued 3,874 thousand shares of common stock under the Long Term Incentive Plan ("LTIP") for the Company Group employees overseas. The issuance of these shares resulted in an increase in share capital of 7,138 million JPY and share premium of 7,138 million JPY. During the year ended March 31, 2023, the Company conducted the disposal of 8,091 thousand treasury shares under LTIP for the Company Group employees overseas. The disposal of treasury shares resulted in a decrease in treasury shares of 27,599 million JPY. The shares of the Company's common stock were converted into the Company's American Depositary Shares ("ADSs") and settled with employees.

During the year ended March 31, 2022, Takeda acquired 22,469 thousand shares of its common stock for 74,973 million JPY in accordance with the resolution on the acquisition of its own shares at the Board of Directors Meeting held on October 28, 2021. During the year ended March 31, 2023, Takeda acquired 6,908 thousand shares of its common stock for 24,993 million JPY, and the acquisition in accordance with the resolution was completed.

Dividends declared and paid	JPY (millions) Total dividends	Dividends per share JPY	Record date	Effective date
April 1, 2020, to March 31, 2021				
Q1 2020	¥ 141,858	¥ 90.00	March 31, 2020	June 25, 2020
Q3 2020	141,860	90.00	September 30, 2020	December 1, 2020
April 1, 2021, to March 31, 2022				
Q1 2021	141,859	90.00	March 31, 2021	June 30, 2021
Q3 2021	142,387	90.00	September 30, 2021	December 1, 2021
April 1, 2022, to March 31, 2023				
Q1 2022	140,365	90.00	March 31, 2022	June 30, 2022
Q3 2022	140,474	90.00	September 30, 2022	December 1, 2022

Dividends declared for which the effective date falls in the following fiscal year are as follows:

Dividends declared	JPY (millions) Total dividends	Dividends per share JPY	Record date	Effective date
April 1, 2023, to March 31, 2024				
Q1 2023	140,475	¥ 90.00	March 31, 2023	June 29, 2023

27. Financial Instruments

Takeda promotes risk management to reduce the financial risks arising from business operations. The principal risks to which Takeda is exposed include market risk, counterparty credit risk, and liquidity risk caused by changes in the market environment such as fluctuations in foreign exchange rates, interest rates and market prices of commodities and other financial holdings. Each of these risks is managed in accordance with Takeda's policies.

Financial Assets and Liabilities

	JPY (millions) As of March 31, 2022					
	Financial assets measured at amortized cost	Measured at fair value through other comprehensive income	Measured at fair value through profit or loss	Derivative hedging instruments	Other financial liabilities	Total
Financial assets measured at fair value						
Other financial assets -						
Equity instruments	¥ —	¥ 148,451	¥ —	¥ —	¥ —	¥ 148,451
Derivative financial instruments	—	—	19,141	22,749	—	41,890
Investments in convertible notes	—	—	10,409	—	—	10,409
Investments in debt instruments	—	—	1,052	—	—	1,052
Financial assets associated with contingent consideration arrangements	—	—	26,852	—	—	26,852
Trade and other receivables	—	20,665	—	—	—	20,665
Total	¥ —	¥ 169,117	¥ 57,454	¥ 22,749	¥ —	¥ 249,320
Financial assets not measured at fair value						
Other financial assets -						
Other	¥ 30,205	¥ —	¥ —	¥ —	¥ —	¥ 30,205
Trade and other receivables	675,979	—	—	—	—	675,979
Cash and cash equivalents	849,695	—	—	—	—	849,695
Total	¥ 1,555,879	¥ —	¥ —	¥ —	¥ —	¥ 1,555,879
Financial liabilities measured at fair value						
Other financial liabilities -						
Derivative financial instruments	¥ —	¥ —	¥ 6,074	¥ 30,455	¥ —	¥ 36,529
Financial liabilities associated with contingent consideration arrangements	—	—	5,844	—	—	5,844
Total	¥ —	¥ —	¥ 11,918	¥ 30,455	¥ —	¥ 42,373
Financial liabilities not measured at fair value						
Other financial liabilities -						
Lease liabilities	¥ —	¥ —	¥ —	¥ —	¥ 465,238	¥ 465,238
Other	—	—	—	—	157,403	157,403
Trade and other payables	—	—	—	—	516,297	516,297
Bonds and loans	—	—	—	—	4,345,410	4,345,410
Total	¥ —	¥ —	¥ —	¥ —	¥ 5,484,348	¥ 5,484,348

	JPY (millions) As of March 31, 2023					
	Financial assets measured at amortized cost	Measured at fair value through other comprehensive income	Measured at fair value through profit or loss	Derivative hedging instruments	Other financial liabilities	Total
Financial assets measured at fair value						
Other financial assets -						
Equity instruments	¥ —	¥ 157,731	¥ —	¥ —	¥ —	¥ 157,731
Derivative financial instruments	—	—	17,131	62,522	—	79,654
Investments in convertible notes	—	—	11,435	—	—	11,435
Investments in debt instruments	—	—	1,063	—	—	1,063
Financial assets associated with contingent consideration arrangements	—	—	23,806	—	—	23,806
Trade and other receivables	—	71,080	—	—	—	71,080
Total	¥ —	¥ 228,811	¥ 53,435	¥ 62,522	¥ —	¥ 344,769
Financial assets not measured at fair value						
Other financial assets -						
Other	¥ 26,168	¥ —	¥ —	¥ —	¥ —	¥ 26,168
Trade and other receivables	578,349	—	—	—	—	578,349
Cash and cash equivalents	533,530	—	—	—	—	533,530
Total	¥ 1,138,047	¥ —	¥ —	¥ —	¥ —	¥ 1,138,047
Financial liabilities measured at fair value						
Other financial liabilities -						
Derivative financial instruments	¥ —	¥ —	¥ 15,261	¥ 25,460	¥ —	¥ 40,721
Financial liabilities associated with contingent consideration arrangements	—	—	8,139	—	—	8,139
Total	¥ —	¥ —	¥ 23,400	¥ 25,460	¥ —	¥ 48,860
Financial liabilities not measured at fair value						
Other financial liabilities -						
Lease liabilities	¥ —	¥ —	¥ —	¥ —	¥ 479,351	¥ 479,351
Other	—	—	—	—	191,595	191,595
Trade and other payables	—	—	—	—	649,233	649,233
Bonds and loans	—	—	—	—	4,382,341	4,382,341
Total	¥ —	¥ —	¥ —	¥ —	¥ 5,702,520	¥ 5,702,520

Fair Value Measurement

Derivative and non-derivative financial instruments measured at fair value are categorized in the following three-tier fair value hierarchy that reflects the significance of the inputs in making the measurements. Level 1 is defined as observable inputs, such as quoted prices in active markets for an identical asset or liability. Level 2 is defined as inputs other than quoted prices in active markets within Level 1 that are directly or indirectly observable. Level 3 is defined as unobservable inputs.

	JPY (millions) As of March 31, 2022			
	Level 1	Level 2	Level 3	Total
Assets:				
Financial assets measured at fair value through profit or loss				
Derivatives	¥ —	¥ 19,141	¥ —	¥ 19,141
Investment in convertible notes	—	—	10,409	10,409
Investment in debt instruments	—	—	1,052	1,052
Financial assets associated with contingent consideration arrangements	—	—	26,852	26,852
Derivatives for which hedge accounting is applied	—	22,749	—	22,749
Financial assets measured at fair value through OCI				
Trade and other receivables	—	20,665	—	20,665
Equity instruments	84,188	—	64,263	148,451
Total	¥ 84,188	¥ 62,556	¥ 102,576	¥ 249,320
Liabilities:				
Financial liabilities measured at fair value through profit or loss				
Derivatives	¥ —	¥ 6,074	¥ —	¥ 6,074
Financial liabilities associated with contingent consideration arrangements	—	—	5,844	5,844
Derivatives for which hedge accounting is applied	—	30,455	—	30,455
Total	¥ —	¥ 36,529	¥ 5,844	¥ 42,373

	JPY (millions) As of March 31, 2023			
	Level 1	Level 2	Level 3	Total
Assets:				
Financial assets measured at fair value through profit or loss				
Derivatives	¥ —	¥ 10,542	¥ 6,589	¥ 17,131
Investment in convertible notes	—	—	11,435	11,435
Investment in debt instruments	—	—	1,063	1,063
Financial assets associated with contingent consideration arrangements	—	—	23,806	23,806
Derivatives for which hedge accounting is applied	—	62,522	—	62,522
Financial assets measured at fair value through OCI				
Trade and other receivables	—	71,080	—	71,080
Equity instruments	74,495	—	83,236	157,731
Total	¥ 74,495	¥ 144,144	¥ 126,129	¥ 344,769
Liabilities:				
Financial liabilities measured at fair value through profit or loss				
Derivatives	¥ —	¥ 8,672	¥ 6,589	¥ 15,261
Financial liabilities associated with contingent consideration arrangements	—	—	8,139	8,139
Derivatives for which hedge accounting is applied	—	25,460	—	25,460
Total	¥ —	¥ 34,131	¥ 14,728	¥ 48,860

Valuation Techniques

The fair value of derivatives classified as Level 2 is measured based on Treasury management system valuation models or the Black-Scholes model, whose significant inputs are based on observable market data.

Derivatives classified as Level 3 include those recognized in connection with settlements of cash flows arising from differences between the fixed prices and floating market prices of renewable energy in a virtual power purchase agreement and those recognized in an agreement to offset the volatility of such cash flows. The fair value of derivatives in Level 3 is measured using the discounted cash flow method. The key assumptions taken into account include forecasted renewable energy prices and the expected generation of the renewable energy generating facility.

The fair value of the investment in convertible notes is measured using techniques such as the discounted cash flow and option pricing models.

The fair value of trade and other receivables, which are due from customers that Takeda has the option to factor, are measured based on the invoiced amount.

Equity investments and investments in debt instruments are not held for trading. If equity instruments or investments in debt instruments are quoted in an active market, the fair value is based on price quotations at the period-end-date. If equity instruments or investments in debt instruments are not quoted in an active market, the fair value is calculated utilizing an adjusted book value per share method or EBITDA multiples approach based on available information as of each period-end-date and comparable companies. The principal input that is not observable and utilized for the calculation of the fair value of equity instruments and investments in debt instruments classified as Level 3 is the EBITDA rate used for the EBITDA multiples approach, which ranges from 3.9 times to 13.7 times. During the years ended March 31, 2022 and 2023, cumulative gains on equity investments of 5,357 million JPY and 6,935 million JPY were reclassified from other comprehensive income to retained earnings, respectively, upon the disposal of certain equity investments in publicly traded companies. The fair value of these investments on the dates of disposal during the years ended March 31, 2022 and 2023 were 16,929 million JPY and 21,800 million JPY, respectively. The investments were disposed of after management's assessment of these investments relative to the investment strategy.

Financial assets and liabilities associated with contingent consideration arrangements are measured at fair value at the time of the divestiture or the acquisition date of business combination. When the contingent consideration arrangement meets the definition of a financial asset or liability, it is subsequently re-measured at fair value at each closing date. The determination of the fair value is based on models such as scenario-based methods and discounted cash flows. The key assumptions take into consideration the probability of meeting each performance target, forecasted revenue projections, and the discount factor. The financial assets associated with contingent consideration arrangements are recognized mainly in relation to the divestiture of XIIDRA. The financial liabilities associated with contingent consideration arrangements are discussed in *Financial liabilities associated with contingent consideration arrangements*.

Transfers between levels

Takeda recognizes transfers between levels of the fair value hierarchy, at the end of the reporting period during which the change has occurred. There were transfers from Level 3 to Level 1 recorded in the years ended March 31, 2022 and 2023. These transfers resulted from the investments in the companies whose shares were previously not listed on an equity or stock exchange and had no recent observable active trades in the shares. During the years ended March 31, 2022 and 2023, the companies listed its equity shares on an exchange and are currently actively traded in the market. As the equity shares have a published price quotation in an active market, the fair value measurement was transferred from Level 3 to Level 1 on the fair value hierarchy during the years ended March 31, 2022 and 2023, respectively. There were no other significant transfers between levels of the fair value hierarchy during the years ended March 31, 2022 and 2023.

Level 3 financial assets fair values

Takeda invests in equity instruments mainly for research collaboration. The following table shows a reconciliation from the opening balances to the closing balances for Level 3 financial asset fair values for the years ended March 31, 2022 and 2023. The disclosure related to Level 3 financial liabilities which are financial liabilities associated with contingent consideration arrangements are included in *Financial liabilities associated with contingent consideration arrangements.* There are no significant changes in fair value during the changes in certain assumptions which influence the fair value measurement for Level 3 financial assets.

	JPY (millions) For the Year Ended March 31			
	2022		2023	
	Financial assets associated with contingent consideration arrangements	Equity instruments	Financial assets associated with contingent consideration arrangements	Equity instruments
As of the beginning of the year	¥ 25,446	¥ 52,468	¥ 26,852	¥ 64,263
Changes recognized as finance income (expenses)	(1,043)	—	1,905	—
Changes in fair value of financial assets associated with contingent consideration due to other elements than time value	—	—	(3,412)	—
Changes in fair value of financial assets measured at fair value through OCI and exchange differences on translation of foreign operations	2,448	23,345	2,182	8,244
Settled and received during the period	—	—	(3,722)	—
Purchases	—	7,919	—	8,527
Sales	—	(644)	—	(22)
Transfers to Level 1	—	(23,856)	—	(1,711)
Acquisition from sale of intangible assets associated with products	—	5,645	—	—
Acquisition from conversion of convertible notes	—	725	—	1,368
Transfers from investments accounted for using the equity method	—	—	—	3,404
Transfers to investments accounted for using the equity method	—	(1,339)	—	(837)
As of the end of the year	¥ 26,852	¥ 64,263	¥ 23,806	¥ 83,236

Financial liabilities associated with contingent consideration arrangements

Financial liabilities associated with contingent consideration arrangements represent consideration related to business combinations or license agreements that are payable only upon future events such as the achievement of development milestones and sales targets, including pre-existing contingent consideration arrangements of the companies that are acquired by Takeda. At each reporting date, the fair value of financial liabilities associated with contingent consideration arrangements is re-measured based on risk-adjusted future cash flows discounted using an appropriate discount rate.

As of March 31, 2022 and 2023, the balance primarily relates to pre-existing contingent consideration arrangements from historical acquisitions.

The fair value of financial liabilities associated with contingent consideration arrangements could increase or decrease due to changes in certain assumptions which underpin the fair value measurements. The assumptions include probability of milestones being achieved.

The fair value of financial liabilities associated with contingent consideration arrangements are classified as Level 3 in the fair value hierarchy. The following table shows a reconciliation from the opening balances to the closing balances and payment term for financial liabilities associated with contingent consideration arrangements for the period ended March 31, 2022 and 2023, respectively. There are no significant changes in fair value during the changes in significant assumptions which influence the fair value measurement for financial liabilities associated with contingent consideration arrangements.

	JPY (millions) For the Year Ended March 31	
	2022	2023
As of the beginning of the year	¥ 27,770	¥ 5,844
Additions arising from business combinations	5,203	—
Reversal from sale of intangible assets associated with products	(11,479)	—
Changes in the fair value during the period	(10,705)	2,605
Settled and paid during the period	(6,293)	(728)
Foreign currency translation differences	1,348	418
As of the end of the year	¥ 5,844	¥ 8,139

	JPY (millions) As of March 31	
	2022	2023
Payment term (undiscounted)		
Within one year	¥ 606	¥ 918
Between one and three years	2,869	4,537
Between three and five years	2,000	2,980
More than five years	980	1,031

Financial instruments not measured at fair value

The carrying amount and fair value of financial instruments that are not measured at fair value in the consolidated statements of financial position are as follows. Fair value information is not provided for financial instruments, if the carrying amount is a reasonable estimate of fair value due to the relatively short period of maturity of these instruments.

	JPY (millions) As of March 31			
	2022		2023	
	Carrying amount	Fair value	Carrying amount	Fair value
Bonds	¥ 3,637,355	¥ 3,630,521	¥ 3,618,314	¥ 3,291,147
Long-term loans	707,770	703,032	723,772	721,419

Long-term financial liabilities are recognized at their carrying amount. The fair value of bonds is measured at quotes whose significant inputs to the valuation model used are based on observable market data. The fair value of loans is measured at the present value of future cash flows discounted using the applicable market rate on the loans in consideration of the credit risk by each group classified in a specified period. The fair value of bonds and long-term loans are classified as Level 2 in the fair value hierarchy.

Market Risk

Major market risks to which Takeda is exposed are 1) foreign currency risk, 2) interest rate risk and 3) price fluctuation risk. Financial instruments affected by market risk include loans and borrowings, deposits, equity investments and derivative financial instruments.

Foreign Currency Risk

Takeda's exposure to foreign exchange rates primarily relates to its foreign currency denominated operations and Takeda's net investments in foreign subsidiaries. Takeda manages foreign currency risks in a centralized manner using derivative financial instruments. Takeda's policy does not permit the use of speculative foreign currency financial instruments or derivatives.

Takeda uses forward exchange contracts, currency swaps, and currency options to hedge individually significant foreign currency transactions. Takeda has also designated loans and bonds denominated in the US dollar and Euro and certain forward exchange contracts as hedging instruments of net investments in foreign operations. As of March 31, 2022 and 2023, the total fair value of the foreign currency denominated loans was 184,520 million JPY and 200,491 million JPY, respectively, and the total fair value of the foreign currency denominated bonds was 2,871,256 million JPY and 2,548,795 million JPY, respectively.

Takeda is exposed mainly to foreign currency risks of the US dollar and Euro. The fair values of Takeda's financial instrument holdings are analyzed to determine their sensitivity to changes in foreign exchange rates. Our analysis shows that if the JPY were to change against all other currencies by 5%, as of March 31, 2022 and 2023, the hypothetical impact on net income would not be material. This analysis assumes that all other variables, in particular interest rates, remain constant and that a change in one currency's rate relative to the JPY would not have any effect on another currency's rate relative to the JPY. In addition, this analysis does not include the effects of foreign currency translation on financial instruments that are denominated in the functional currency of the entity holding them.

	JPY (millions) As of March 31, 2022		
	Contract amount	Contract amount to be settled in more than one year	Fair value
Forward exchange contracts:			
Selling:			
Euro	¥ 243,870	¥ —	¥ (11,315)
United States Dollar	445,285	—	(8,181)
Buying:			
Euro	244,041	—	11,326
United States Dollar	360,656	—	4,894
Currency swaps:			
Buying:			
United States Dollar	717,114	717,114	8,686

	JPY (millions) As of March 31, 2023		
	Contract amount	Contract amount to be settled in more than one year	Fair value
Forward exchange contracts:			
Selling:			
Euro	¥ 975,368	¥ —	¥ (4,799)
United States Dollar	179,942	—	(341)
Buying:			
Euro	1,056,070	—	31
Currency swaps:			
Buying:			
United States Dollar	717,114	717,114	41,044

The above currency swaps, designated as hedging instruments in a cash flow hedge, were related to foreign currency denominated bonds and loans. The cash flow hedge reserve related to the currency swaps were reclassified to profit or loss in the same period as the hedged expected future cash flows occur.

Interest Rate Risk

Takeda's exposure to the risk of changes in benchmark interest rates and foreign exchange rate relates to the outstanding debts with floating interest rates as well as the trade and other receivables due from customers that Takeda has the option to factor. Takeda uses interest rate swaps, forward interest rate contracts, and cross currency interest rate swaps that fix the amount of future payments to manage interest and foreign exchange rate risks through cash flow hedge strategies. Takeda may also use derivatives that effectively convert its fixed rate debt to floating through fair-value hedge strategies. The following summarizes interest rate swaps, forward interest rate contracts, and cross currency interest rate swaps designated as cash flow hedges as of March 31:

	JPY (millions) As of March 31		
	Contract amount	Contract amount to be settled in more than one year	Fair value
2022	¥ 787,370	¥ 787,370	¥ 8,637
2023	1,098,862	1,048,862	44,042

The fair values of Takeda's financial instrument holdings are analyzed to determine their sensitivity to interest rate changes. Our analysis shows that if there were a 1% change in interest rates, as of March 31, 2022 and 2023, the hypothetical impact on net income would not be material. This analysis assumes that all other variables, in particular foreign currency exchange rates, remain constant.

Price Fluctuation Risk Management

Commodity Price Risk

For its business operations, Takeda is exposed to risks from commodity price fluctuations. Takeda manages this risk primarily by utilizing fixed price contracts but may also use financial instruments to lock in a fixed price.

Market Price Risk

Market pricing and valuations of Takeda's fixed-income financial assets and liabilities are impacted by changes in currency rates, interest rates and credit spreads, which are managed as described above. For equity instruments, Takeda manages the risk of price fluctuations in the instruments by regularly reviewing share prices and financial positions of the issuers.

Our analysis shows that if the market price of equity instruments held by Takeda and investments in trusts which hold equity instruments on behalf of Takeda had changed by 10%, as of March 31, 2022 and 2023, the hypothetical impact on other comprehensive income would not be material. This analysis assumes that all other variables, in particular interest rates and foreign currency exchange rates, remain constant. There is no impact on net income because the changes in the fair value of equity instruments are recognized directly in equity.

Derivative Financial Instruments

As described above, Takeda is exposed to effects related to foreign exchange fluctuations in connection with our international business activities that are denominated in various currencies and Takeda's overseas entities that have different functional currencies. Takeda is also exposed to currency and interest rate fluctuations on our borrowings that we use to finance our business operations and our acquisitions. In addition, Takeda is exposed to interest rate fluctuations on the trade and other receivables due from customers that Takeda has the option to factor. These are denominated in various currencies and may bear interest at variable rates, resulting in the risk related to the currency and interest rate movements.

In order to manage the risk of currency exchange rate and interest rate fluctuations, Takeda may enter into derivative contracts with highly rated financial institutions. Takeda enters into derivative contracts based on our risk management policies, which determine the authority for entering into such transactions and the transaction limits. The policy, which has been consistently followed, is that financial derivatives be used only for hedging foreign currency and interest rate exposure and not for speculative purposes.

Takeda generally designates its derivatives as hedges for accounting purposes. In certain instances, Takeda enters into derivative contracts ("balance sheet hedges") that do not qualify for hedge accounting but are nevertheless utilized to manage the underlying foreign currency exposure risk. Balance sheet hedges are used to offset the foreign currency impact from assets and liabilities on Takeda balance sheet that are denominated in non-functional currencies. Given these foreign currency derivatives work on an offset basis they do not require hedge accounting. Takeda has established guidelines for risk assessment procedures and controls for the use of financial instruments. These guidelines include a clear segregation of duties between execution and administration, and then again between accounting and controlling.

Summary of Financial Position and Financial Performance for Derivative and Hedging Activities

The following tables represent the items designated as hedging instruments, amounts within other components of equity related to items designated as hedged items and amounts of changes in fair value of hedging instruments recorded in other comprehensive income and the amounts reclassified from the hedging reserve to profit or loss as of and for the year ended March 31, 2022:

		JPY (millions) As of March 31, 2022			
	Notional	Carrying amount – assets	Carrying amount – liabilities	Line item in the statement of financial position where hedging instrument is included	Average rate used for the fair value of the hedging instrument
Cash flow hedges					
Interest risk					
Interest rate swaps	575 million USD	¥ —	¥ 49	Other financial liabilities	2.83 %
Currency and interest risk					
Currency and interest rate swaps	6,675 million USD	22,749	14,063	Other financial assets / liabilities	107.43 JPY 1.85%
Net investment hedges					
Foreign currency denominated bonds and loans	5,108 million USD	—	624,138	Bonds and loans	
	7,368 million EUR	—	1,001,896	Bonds and loans	
Forward exchange contracts	594 million USD	—	4,982	Other financial liabilities	
	1,815 million EUR	—	11,360	Other financial liabilities	

	JPY (millions) As of March 31, 2022	
	Balance in cash flow hedges and net investment hedges	Balance in hedge cost reserve
Cash flow hedges		
Interest risk		
Interest rate swaps	¥ 425	¥ —
Forward interest rate	(21,313)	—
Currency and interest risk		
Currency and interest rate swaps	(48,573)	(6,135)
Currency risk		
Hedge related to acquisition	3,560	—
Net investment hedges		
Foreign currency denominated bonds and loans	97,977	—
Forward exchange contracts	54,778	—

	JPY (millions) For the year ended March 31, 2022				
	Amounts recognized in OCI		Amount reclassified to profit or loss		
	Change in fair value of hedging instruments	Hedging costs	Cash flow hedge	Hedging costs	Line item in which reclassification adjustment is included
Cash flow hedges					
Interest risk					
Interest rate swaps	¥ 3,992	¥ —	¥ 1,398	¥ —	Financial expenses
Forward interest rate	(605)	—	2,312	—	Financial expenses
Currency and interest risk					
Currency and interest rate swaps	79,394	6,611	(83,031)	(3,071)	Financial income and Financial expenses
Net investment hedges					
Foreign currency denominated bonds and loans	107,064	—	—	—	
Forward exchange contracts	35,646	—	—	—	

The following tables represent the items designated as hedging instruments, amounts within other components of equity related to items designated as hedged items and amounts of changes in fair value of hedging instruments recorded in other comprehensive income and the amounts reclassified from the hedging reserve to profit or loss as of and for the year ended March 31, 2023:

		JPY (millions) As of March 31, 2023			
	Notional	Carrying amount – assets	Carrying amount – liabilities	Line item in the statement of financial position where hedging instrument is included	Average rate used for the fair value of the hedging instrument
Cash flow hedges					
Interest risk					
Interest rate swaps	575 million USD	¥ 5,148	¥ —	Other financial assets	2.83 %
	75,000 million JPY	—	50	Other financial liabilities	0.56 %
Forward interest rate	230,000 million JPY	—	2,100	Other financial liabilities	0.54 %
Currency and interest risk					
Currency and interest rate swaps	6,675 million USD	55,223	14,179	Other financial assets / liabilities	107.43 JPY 1.85%
Net investment hedges					
Foreign currency denominated bonds and loans	4,086 million USD	—	545,327	Bonds and loans	
	6,591 million EUR	—	957,993	Bonds and loans	
Forward exchange contracts	1,368 million USD	728	1,069	Other financial assets / liabilities	
	4,384 million EUR	1,424	8,062	Other financial assets / liabilities	

	JPY (millions) As of March 31, 2023	
	Balance in cash flow hedges and net investment hedges	Balance in hedge cost reserve
Cash flow hedges		
Interest risk		
Interest rate swaps	¥ 2,948	¥ —
Forward interest rate	(21,182)	—
Currency and interest risk		
Currency and interest rate swaps	(72,678)	(23,127)
Currency risk		
Hedge related to acquisition	3,560	—
Net investment hedges		
Foreign currency denominated bonds and loans	188,343	—
Forward exchange contracts	80,584	—

	JPY (millions) For the year ended March 31, 2023				
	Amounts recognized in OCI		Amount reclassified to profit or loss		
	Change in fair value of hedging instruments	Hedging costs	Cash flow hedge	Hedging costs	Line item in which reclassification adjustment is included
Cash flow hedges					
Interest risk					
Interest rate swaps	¥ 3,993	¥ —	¥ (360)	¥ —	Financial income
Forward interest rate	(2,123)	—	2,312	—	Financial expenses
Currency and interest risk					
Currency and interest rate swaps	54,566	(21,426)	(89,289)	(3,052)	Financial income and Financial expenses
Net investment hedges					
Foreign currency denominated bonds and loans	142,456	—	—	—	
Forward exchange contracts	25,806	—	—	—	

The amount relating to the ineffectiveness recorded in profit or loss was immaterial for the years ended March 31, 2022 and 2023. The amount of hedging gains/losses recorded in other comprehensive income and reclassified to profit or loss as hedged future cash flows were no longer expected to occur was immaterial for the years ended March 31, 2022 and 2023.

Capital Management

The capital structure of Takeda consists of shareholders' equity (Note 26), bonds and loans (Note 20), and cash and cash equivalents (Note 18). The fundamental principles of Takeda's capital risk management are to build and maintain a steady financial base for the purpose of maintaining soundness and efficiency of operations and achieving sustainable growth. According to these principles, Takeda conducts capital investment, profit distribution such as dividends, and repayment of loans based on steady operating cash flows through the development and sale of competitive products.

Takeda utilizes factoring arrangements for selected trade receivables. Under this program, trade receivables sold are derecognized when the risks and rewards of ownership have been transferred. Amounts due from customers that are subject to the factoring arrangements but have not been factored at fiscal year end are disclosed in Note 17.

Takeda balances and monitors its capital structure between debt and equity and adheres to a conservative financial discipline.

Credit Risk

Takeda is exposed to credit risk from its operating activities (primarily trade receivables) and from its financing activities, including deposits with banks and financial institutions, foreign exchange transactions, and other financial instruments. The maximum exposure to credit risk, without taking into account any collateral held at the end of the reporting period, is represented by the carrying amount of the financial instruments which is exposed to credit risk on the consolidated statements of financial position. Takeda regularly monitors the status of credit risk exposure with banks and financial institutions.

Customer Credit Risk

Trade and other receivables are exposed to customer credit risk. Takeda monitors the status of overdue balances, reviews outstanding balances for each customer and regularly examines the credibility of major customers in accordance with Takeda's policies for credit management to facilitate the early evaluation and the reduction of potential credit risks. In parallel, Takeda utilizes programs to sell certain trade and other receivables due from certain customers to a select group of banks on a non-recourse basis which in turn minimizes the credit risk associated with such customers. If necessary, Takeda obtains rights to collateral or guarantees on the receivables.

The following represents the carrying amount of the trade receivables categorized by due date and the analysis of impairment loss allowance as of March 31, 2022 and 2023:

	JPY (millions) except for percentage As of March 31, 2022						
		Amount past due					
	Current	Within 30 days	Over 30 days but within 60 days	Over 60 days but within 90 days	Over 90 days but within one year	Over one year	Total
Gross carrying amount	¥ 569,289	¥ 19,369	¥ 5,972	¥ 3,670	¥ 14,391	¥ 14,217	¥ 626,908
Impairment loss allowance	(3,274)	(23)	(88)	(50)	(963)	(4,993)	(9,390)
Net carrying amount	566,015	19,346	5,884	3,620	13,428	9,224	617,518
Weighted average loss rate	0.6 %	0.1 %	1.5 %	1.4 %	6.7 %	35.1 %	1.5 %

	JPY (millions) except for percentage As of March 31, 2023						
		Amount past due					
	Current	Within 30 days	Over 30 days but within 60 days	Over 60 days but within 90 days	Over 90 days but within one year	Over one year	Total
Gross carrying amount	¥ 499,795	¥ 23,676	¥ 14,999	¥ 8,975	¥ 19,912	¥ 15,430	¥ 582,787
Impairment loss allowance	(2,219)	(66)	(66)	(33)	(694)	(4,278)	(7,356)
Net carrying amount	497,576	23,610	14,933	8,942	19,218	11,152	575,431
Weighted average loss rate	0.4 %	0.3 %	0.4 %	0.4 %	3.5 %	27.7 %	1.3 %

Management believes that the unimpaired amounts that are past due are still collectible in full, based on historical payment behavior and extensive analysis of customer credit risk.

As of March 31, 2022 and 2023, Takeda has provided loss allowance on trade receivables and other receivables not past due based on an analysis of credit histories. Loss allowance for trade receivables are measured based on expected credit losses on a collective basis using the simplified approach. However, when events that have a detrimental impact on the estimated future cash flows such as customers' deterioration of financial conditions or failure of payment overdue have occurred, expected credit losses are measured on an individual basis as credit-impaired financial assets. Takeda considers a financial asset to be in default when the customer is unlikely to pay the obligation in full, without recourse by Takeda to take actions such as realizing collaterals, if any.

The following is a summary of the change in the impairment loss allowance for trade receivables for the years ended March 31, 2022 and 2023. The impairment loss allowance recognized for other than trade receivables is immaterial.

	JPY (millions)		
	Bad debt provision calculated by simplified approach	Bad debt provision recognized to credit-impaired financial assets	Total
As of April 1, 2021	¥ 2,359	¥ 6,278	¥ 8,637
Increases	999	1,837	2,836
Decreases (written off)	(60)	(2,147)	(2,207)
Decreases (reversed)	(333)	(533)	(866)
Foreign currency translation differences	446	544	990
As of March 31, 2022	¥ 3,411	¥ 5,979	¥ 9,390
Increases	92	190	282
Decreases (written off)	(719)	(2,509)	(3,228)
Decreases (reversed)	(119)	(213)	(332)
Foreign currency translation differences	662	582	1,244
As of March 31, 2023	¥ 3,327	¥ 4,029	¥ 7,356

Other Counterparty Credit Risk

Cash reserves of Takeda are concentrated mostly with the Company and entities acting as the cash pool leader in the U.S. and Europe. These cash reserves are primarily managed exclusively by investments in highly rated short-term bank deposits and bonds of highly rated issuers within the investment limits determined by reviewing the investment ratings and terms under Takeda's policies for fund management, resulting in limited credit risk. Cash reserves, other than those subject to the group cash pooling system, are managed by each consolidated subsidiary in accordance with the Company's fund management policies. For derivatives, Takeda enters into contracts only with financial counterparties rated investment grade or higher in order to minimize counterparty risk.

Liquidity Risk

Takeda manages liquidity risk and establishes an adequate management framework for liquidity risk to secure stable short-, mid-, and long-term funds and sufficient liquidity for operations. Takeda manages liquidity risk by monitoring forecasted cash flows and actual cash flows on an ongoing basis. In addition, Takeda has commitment lines with some counterparty financial institutions to manage liquidity risk (Note 20). Takeda strives to maximize the available liquidity with a combination of liquid short-term investments and committed credit lines with strong rated counterparties. The objective is to maintain levels in excess of project cash needs to mitigate the risk of contingencies.

The table below presents the balances of financial liabilities by maturity. The total contract amount below reflects cash flows presented on an undiscounted cash flow basis, including interest expense. The amounts disclosed as of March 31, 2022 and 2023 are undiscounted cash flows using the respective spot foreign exchange rates as of March 31, 2022 and 2023.

	JPY (millions)							
	Carrying amount	Total	Within one year	Between one and two years	Between two and three years	Between three and four years	Between four and five years	More than five years
As of March 31, 2022								
Bonds and loans								
Bonds	¥ 3,637,355	¥ 4,648,070	¥ 221,182	¥ 395,333	¥ 580,073	¥ 167,299	¥ 632,188	¥ 2,651,995
Loans	708,055	733,219	78,155	103,540	54,623	90,696	105,942	300,263
Trade and other payables	516,297	516,297	516,297	—	—	—	—	—
Lease liabilities	465,238	645,782	53,877	52,489	48,660	44,907	39,502	406,347
Derivative liabilities	36,529	(48,275)	21,144	(1,390)	(2,090)	(2,405)	(2,647)	(60,887)
Derivative assets	(41,890)	(151,044)	(26,505)	(7,060)	(9,183)	(9,183)	(9,573)	(89,540)
As of March 31, 2023								
Bonds and loans								
Bonds	¥ 3,658,314	¥ 4,640,222	¥ 331,223	¥ 586,179	¥ 182,261	¥ 685,321	¥ 164,573	¥ 2,690,665
Loans	724,027	767,558	113,404	60,482	92,999	107,483	317,706	75,484
Trade and other payables	649,233	649,233	649,233	—	—	—	—	—
Lease liabilities	479,351	665,983	59,623	56,009	51,229	46,111	41,281	411,730
Derivative liabilities	40,721	(64,835)	15,858	(509)	(2,324)	(2,231)	(2,243)	(73,386)
Derivative assets	(79,654)	(234,200)	(28,814)	(17,443)	(13,297)	(13,302)	(33,858)	(127,486)

The contractual amount of bonds in “Between two and three years” as of March 31, 2022 and “Between one and two years” as of March 31, 2023, includes 500,000 million JPY principal amount of the hybrid subordinated bonds (the “Hybrid Bonds”) as Takeda may make an early repayment of all of the principal of the Hybrid Bonds on each interest payment date beginning October 6, 2024. For details on the principal and interest rates associated with these bonds and loans, see Note 20.

Reconciliation of liabilities arising from financing activities

	JPY (millions)						
	Bonds	Long-term loans	Short-term loans	Lease liabilities	Derivative assets used for hedge of debts	Derivative liabilities used for hedge of debts	Total
As of April 1, 2021	¥ 3,532,202	¥ 1,103,100	¥ 69	¥ 436,412	¥ (1,506)	¥ 58,293	¥ 5,128,570
Cash flows from financing activities							
Net increase (decrease) in short-term loans and commercial papers	—	—	(2)	—	—	—	(2)
Proceeds from issuance of bonds	249,334	—	—	—	—	—	249,334
Repayments of long-term loans	—	(414,105)	—	—	—	—	(414,105)
Repayments of bonds	(395,106)	—	—	—	—	(903)	(396,009)
Repayments of lease liabilities	—	—	—	(39,694)	—	—	(39,694)
Interest paid	—	—	—	(13,934)	—	—	(13,934)
Non-cash items							
Foreign exchange movement	237,833	18,737	219	34,701	—	—	291,490
Change in fair value	—	—	—	—	(21,243)	(43,327)	(64,570)
New, amended and terminated leases	—	—	—	33,819	—	—	33,819
Others	13,092	39	—	13,934	—	—	27,065
As of March 31, 2022	¥ 3,637,355	¥ 707,770	¥ 285	¥ 465,238	¥ (22,749)	¥ 14,063	¥ 4,801,964

	JPY (millions)						
	Bonds	Long-term loans	Short-term loans	Lease liabilities	Derivative assets used for hedge of debts	Derivative liabilities used for hedge of debts	Total
As of April 1, 2022	¥ 3,637,355	¥ 707,770	¥ 285	¥ 465,238	¥ (22,749)	¥ 14,063	¥ 4,801,964
Cash flows from financing activities							
Net increase (decrease) in short-term loans and commercial papers	40,000	—	—	—	—	—	40,000
Proceeds from long-term loans	—	75,000	—	—	—	—	75,000
Repayments of long-term loans	—	(75,181)	—	—	—	—	(75,181)
Repayments of bonds	(281,489)	—	—	—	—	—	(281,489)
Repayments of lease liabilities	—	—	—	(43,401)	—	—	(43,401)
Interest paid	—	—	—	(16,580)	—	—	(16,580)
Non-cash items							
Foreign exchange movement	253,390	16,135	25	32,173	—	—	301,723
Change in fair value	—	—	—	—	(32,474)	116	(32,358)
New, amended and terminated leases	—	—	—	25,341	—	—	25,341
Others	9,058	48	(54)	16,580	—	—	25,632
As of March 31, 2023	¥ 3,658,314	¥ 723,772	¥ 256	¥ 479,351	¥ (55,223)	¥ 14,179	¥ 4,820,649

Others includes an increase in debts due to application of amortized cost method.

28. Share-based Payments

Takeda maintains share-based compensation payment plans for the benefit of its directors and certain employees of the Company and its subsidiaries and affiliates worldwide. Takeda recorded total compensation expense related to its share-based payment plans of 39,428 million JPY, 43,730 million JPY, and 61,024 million JPY for the years ended March 31, 2021, 2022 and 2023, respectively, in its consolidated statements of profit or loss.

Equity-settled Plans

Stock Options

Takeda previously provided a stock option plan under which it granted awards to members of Takeda's board of directors (the "Board"), corporate officers, and senior management through the year ended March 31, 2014. There were no stock options granted during the years presented in these financial statements and all previously granted awards are fully vested. These awards generally vested three years after the grant date. The stock options are exercisable for 10 years after the grant date for options held by members of the Board and 20 years for options held by corporate officers and senior management. The individual must be either a Board member or an employee of the Company or one of its subsidiaries or affiliates to exercise the options, unless the individual retired due to the expiration of their term of office, mandatory retirement or other acceptable reasons.

There was no compensation expense recorded during the years ended March 31, 2021, 2022 and 2023 as all awards were fully vested.

The following table summarizes the stock option activity:

	For the Year Ended March 31					
	2021		2022		2023	
	Number of options (shares)	Weighted average exercise price (JPY)	Number of options (shares)	Weighted average exercise price (JPY)	Number of options (shares)	Weighted average exercise price (JPY)
As of beginning of the year	3,371,200	¥ 4,065	3,357,200	¥ 4,082	3,347,100	¥ 4,094
Exercised	(14,000)	1	(10,100)	1	(43,500)	2,802
As of end of the year	3,357,200	4,082	3,347,100	4,094	3,303,600	4,111

All of the stock options were exercisable as of March 31, 2021, 2022 and 2023.

The weighted-average share price at the date of exercise was 4,115 JPY, 3,815 JPY and 3,852 JPY during the years ended March 31, 2021, 2022 and 2023, respectively. The weighted-average exercise price and weighted-average remaining contractual life of the share options outstanding were 4,082 JPY and 11 years, 4,094 JPY and 10 years, and 4,111 JPY and 9 years, as of March 31, 2021, 2022 and 2023, respectively.

Stock Incentive Plans

Takeda has the following 3 stock-based incentive compensation plans for its directors and eligible employees including members of senior management:

Board incentive plan ("BIP") Trust -The BIP Trust is an incentive plan for board directors designed based on Restricted Stock Units and Performance Share Units, whereby Restricted Stock Unit awards and Performance Share Unit awards are granted to board directors. Each award is settled in a single share of the Company's common stock. Under the BIP, Restricted Stock Unit awards are subject to certain service-based conditions and vest ratably over three years. Performance Share Unit awards are granted to internal directors and are subject to certain service-based conditions and also subject to the achievement of certain performance metrics that are intended to align with Takeda's strategic focus and long-term growth. Performance Share Unit awards vest three years from the date of grant. For purposes of the Performance Share Unit awards, the performance metrics primarily consisted of: (i) 3-year accumulated revenue; (ii) 3-year accumulated core operating profit margin; (iii) 3-year accumulated free cash flow; (iv) certain R&D goals; and (v) 3-year relative total shareholder return. The settlement value of the awards is based on stock price and subject to, among other things, applicable tax withholding, foreign exchange rates (in countries other than Japan) and the value of company dividends during the vesting period. Takeda, through a wholly owned trust, buys shares of the Company's common stock in the market on the grant date, and uses these shares to settle the awards upon vesting. The number of shares the individual receives (either through physical settlement or cash) is based on the achievement of the performance criteria and vesting of the award. The trust settles the awards through the issuance of shares to individuals residing in Japan. For individuals residing outside of Japan, the trust sells the shares the individual is eligible to receive and pays cash to the individual in settlement of the award.

Employee Stock Ownership Plan ("ESOP") Trust - The ESOP Trust is an employee incentive plan designed based on Restricted Stock Units and Performance Share Units, whereby Restricted Stock Unit awards and Performance Share Unit awards are granted to certain employees, including members of senior management of the Company. Each award is settled in a single share of the Company's common stock. Restricted Stock Unit awards and Performance Share Unit awards are granted to certain members of senior management while Restricted Stock Unit awards are granted to the remainder of employees. Restricted Stock Unit awards are subject to certain service-based conditions and vest ratably over three years. Performance Share Unit awards are subject to certain service-based conditions and also subject to the achievement of certain performance metrics that are intended to align with Takeda's strategic focus and long-term growth. Performance Share Unit awards vest three years from the date of grant. For purposes of the Performance Share Unit awards, the performance metrics primarily consisted of (i) 3-year accumulated revenue; (ii) 3-year

accumulated core operating profit margin; (iii) 3-year accumulated free cash flow; (iv) certain R&D goals; and (v) 3-year relative total shareholder return. The settlement value of the awards is based on stock price and subject to, among other things, applicable tax withholding and the value of company dividends during the vesting period. Takeda, through a wholly owned trust, buys shares of the Company's common stock in the market or issues shares the Company's common stock on the grant date and uses these shares to settle the awards upon vesting. The number of shares the individual receives is based on the achievement of the performance criteria and vesting of the award. The trust settles the awards through the issuance of shares to individuals residing in Japan. For individuals residing outside of Japan, the trust sells the shares the individual is eligible to receive and pays cash to the individual in settlement of the award.

Long-Term Incentive Plan for Company Group Employees Overseas ("LTIP") - The LTIP was approved by the Board on June 24, 2020 and is an incentive plan that provides for the grant of awards to eligible employees, including members of senior management of the Company and its subsidiaries and affiliates overseas. The LTIP provides for the grant of Restricted Stock Units and Performance Stock Units, as well other equity based awards. Grants under the LTIP may be settled in American Depositary Shares ("ADSs") or cash, or a combination thereof.
Takeda first granted awards under the LTIP on July 1, 2020 in the form of Restricted Stock Unit awards and Performance Stock Unit awards, and no other forms of awards have been granted under the LTIP to date. Restricted Stock Unit awards are subject to certain service-based conditions and vest ratably over three years. Performance Stock Unit awards are subject to certain service-based conditions and also subject to the achievement of certain performance metrics that are intended to align with Takeda's strategic focus and long-term growth. Performance Stock Unit awards vest three years from the date of grant. For purposes of the Performance Stock Unit awards, the performance metrics primarily consisted of: (i) 3-year accumulated revenue; (ii) 3-year accumulated core operating profit margin; (iii) 3-year accumulated free cash flow; (iv) certain R&D goals; and (v) 3-year relative total shareholder return. The value of such awards when such awards are to be settled in ADSs is based on the fair market value of the shares of the Company's common stock converted into ADSs, subject to, among other things, applicable tax withholding, foreign exchange rates and the value of company dividends during the vesting period. Restricted Stock Unit awards and Performance Stock Unit awards granted under the LTIP are to be settled in ADS to award recipients residing and employed in countries outside of Japan where settlement in ADSs is permitted by local law and regulation. In countries outside of Japan where such form of settlement is not permissible due to legal, regulatory and/or administrative reasons, Restricted Stock Unit awards and Performance Stock Unit awards are structured such that settlement is to be made in cash and accounted as a "Cash-Settled LTIP Award" (please refer to Cash-Settled LTIP Awards).

The total compensation expense recognized related to these plans was 37,663 million JPY, 43,374 million JPY and 60,672 million JPY during the years ended March 31, 2021, 2022 and 2023, respectively.

The weighted average fair value of the awards at the grant date is as follows (in JPY):

	For the Year Ended March 31		
	2021	2022	2023
BIP:			
Weighted average fair value at grant date	¥ 3,765	¥ 3,738	¥ 3,759
ESOP:			
Weighted average fair value at grant date	3,765	3,738	3,759
Equity-Settled LTIP:			
Weighted average fair value at grant date	1,907 (US$17.64 in contractual currency)	1,877 (US$16.90 in contractual currency)	1,909 (US$14.09 in contractual currency)

The grant date fair value for BIP and ESOP was calculated using the share price of the Company's common stock on the grant date while the grant date fair value for LTIP was calculated using the share price of ADS as it was determined to be approximately the same as the fair value of the awards. One ADS equals 0.5 of the Company's common stock.

The following table summarizes the award activity related to the BIP (the number of awards) (1 award represents 1 share of the Company's common stock), ESOP (the number of awards) (1 award represents 1 share of the Company's common stock) and Equity-settled LTIP (the number of awards) (1 award represents 1 share of the ADS). One ADS equals 0.5 of the Company's common stock:

	For the Year Ended March 31								
	2021			2022			2023		
	BIP	ESOP	Equity-Settled LTIP	BIP	ESOP	Equity-Settled LTIP	BIP	ESOP	Equity-Settled LTIP
At beginning of the year	819,229	13,398,751	—	1,035,843	7,751,952	23,412,994	1,216,361	3,372,452	40,861,734
Granted	518,965	791,687	25,223,010	536,121	534,437	29,211,506	544,491	450,340	38,897,622
Forfeited/expired before vesting	—	(794,005)	(1,744,170)	—	(552,490)	(4,270,590)	(13,554)	(96,015)	(4,682,948)
Settled	(302,351)	(5,644,481)	—	(355,603)	(4,361,447)	(7,466,212)	(435,309)	(2,949,200)	(15,237,880)
Transfer to Cash-Settled LTIP	—	—	(65,846)	—	—	(25,964)	—	—	(85,930)
Transfer to Cash-Settled RSU	—	—	—	—	—	—	—	(3,733)	—
At end of the year	1,035,843	7,751,952	23,412,994	1,216,361	3,372,452	40,861,734	1,311,989	773,844	59,752,598

There were no exercisable shares as of March 31, 2021, 2022, and 2023. The weighted average remaining contractual life of the outstanding awards was one year for the BIP as of March 31, 2022 and 2023, zero year as of March 31, 2022 and one year as of March 31, 2023 for the ESOP, and one year for the Equity-Settled LTIP plans as of March 31, 2022 and 2023.

Cash-Settled Awards

Takeda has a phantom stock appreciation rights ("PSARs") plan and a restricted stock units ("RSUs") plan for certain employees of subsidiaries of the Company. The value of these awards is linked to share price of the Company and are settled in cash. Moreover, where settlement of awards granted under the LTIP described under "—Equity Settled Plans" above in ADSs or shares of common stock is not permissible due to legal, regulatory and/or administrative reasons, such awards are settled in cash. The total compensation expense recorded associated with these plans was 1,765 million JPY, 356 million JPY and 352 million JPY during the years ended March 31, 2021, 2022 and 2023. The total liability reflected in the consolidated statements of financial position as of March 31, 2021, 2022 and 2023 is 2,115 million JPY, 1,583 million JPY and 1,026 million JPY, respectively.

Phantom stock appreciation rights ("PSARs")

The PSARs vest one third each year over a three-year period from the end of the fiscal year during which the awards were granted and can be exercised for a period of ten years from the end of the fiscal year during which the awards were granted. The awards are settled through a cash payment to the holder based on the difference between the share price of the Company at the date of exercise, and the share price at the date of grant.

The following table summarizes the award activity related to the PSARs (the number of awards) (1 award represents 1 share of the Company's common stock) :

	For the Year Ended March 31					
	2021		2022		2023	
	Number of PSARs	Weighted average exercise price (JPY)	Number of PSARs	Weighted average exercise price (JPY)	Number of PSARs	Weighted average exercise price (JPY)
As of beginning of the year	2,686,749	¥ 4,873	2,270,439	¥ 4,997	1,471,095	¥ 5,481
Forfeited/expired after vesting	(416,310)	4,641	(799,344)	5,134	(1,253,565)	6,054
As of end of the year	2,270,439	4,997	1,471,095	5,481	217,530	5,956

All PSARs were vested and exercisable as of March 31, 2021, 2022 and 2023. There was no intrinsic value of vested cash-settled share-based payments as of March 31, 2022 and 2023.

Restricted stock units (RSUs)

The RSUs vest one third each year over a three-year period from the end of the fiscal year during which the awards were granted. The RSUs are settled upon vesting based on the share price at the vesting date plus any dividends paid on shares during the vesting period. There is no exercise price payable by the holder.

The following table summarizes the award activity related to the RSUs (the number of awards) (1 award represents 1 share of the Company's common stock):

	For the Year Ended March 31		
	2021	2022	2023
As of the beginning of the year	1,439,536	778,451	317,734
Granted	23,541	—	—
Forfeited/expired before vesting	(155,551)	(62,649)	(8,208)
Settled	(529,075)	(398,068)	(313,259)
Transfer from Equity-Settled ESOP	—	—	3,733
As of the end of the year	778,451	317,734	—

There are no exercisable balances as of March 31, 2021, 2022 and 2023.

Cash-Settled LTIP Awards

As noted above, for purposes of restricted stock unit awards and performance stock units granted under the LTIP in countries where settlement in ADSs is not permissible due to legal, regulatory and/or administrative reasons, such grants are structured such that settlement is to be made in cash and accounted for as Cash-Settled LTIP Awards.

The following table summarizes the award activity related to the Cash-Settled LTIP Awards (the number of awards) (1 award represents 1 ADS):

	For the Year Ended March 31		
	2021	2022	2023
As of the beginning of the year	—	262,994	296,640
Granted	286,316	153,604	213,224
Forfeited/expired before vesting	(29,478)	(25,682)	(30,372)
Settled	(59,690)	(120,240)	(197,780)
Transfer from Equity-Settled LTIP	65,846	25,964	85,930
As of the end of the year	262,994	296,640	367,642

There are no exercisable balances as of March 31, 2021, 2022 and 2023.

29. Subsidiaries and Associates

The number of consolidated subsidiaries decreased by 25 in the year ended March 31, 2023, primarily due to mergers and liquidations to reorganize capital in subsidiaries acquired as part of integration with Shire. The number of associates accounted for using the equity method decreased by 2 primarily due to a change of ownership ratio.

The following is a listing of the Company's consolidated subsidiaries (including partnerships) as of March 31, 2023:

Company name	Country	Ownership of Voting Rights (%)
Takeda Argentina S.A.	Argentina	100.0%
Takeda Austria GmbH	Austria	100.0%
Takeda Manufacturing Austria AG	Austria	100.0%
Baxalta Innovations GmbH	Austria	100.0%
Takeda Distribuidora Ltda.	Brazil	100.0%
Takeda Pharma Ltda.	Brazil	100.0%
Takeda Canada Inc.	Canada	100.0%
Takeda (China) Holdings Co., Ltd.	China	100.0%
Takeda (China) International Trading Co., Ltd.	China	100.0%
Tianjin Takeda Pharmaceuticals Co., Ltd	China	100.0%
Takeda France S.A.S.	France	100.0%
Takeda GmbH	Germany	100.0%
Takeda Ireland Limited	Ireland	100.0%
Shire Pharmaceuticals International Unlimited Company	Ireland	100.0%
Shire Acquisitions Investments Ireland Designated Activity Company	Ireland	100.0%
Shire Ireland Finance Trading Limited	Ireland	100.0%
Takeda Italia S.p.A.	Italy	100.0%
Takeda Pharmaceuticals Korea Co., Ltd.	Korea	100.0%
Takeda Mexico S.A.de C.V.	Mexico	100.0%
Takeda Nederland B.V.	Nederland	100.0%
Takeda Pharmaceuticals Limited Liability Company	Russia	100.0%
Takeda Development Center Asia, Pte. Ltd.	Singapore	100.0%
Takeda Manufacturing Singapore	Singapore	100.0%
Takeda Farmaceutica Espana S.A.	Spain	100.0%
Takeda Pharma AB	Sweden	100.0%
Takeda Pharmaceuticals International AG	Switzerland	100.0%
Baxalta Manufacturing, S.a r.l.	Switzerland	100.0%
Takeda Pharma AG	Switzerland	100.0%
Takeda UK Limited	United Kingdom ("U.K.")	100.0%
Takeda Pharmaceuticals U.S.A., Inc.	U.S.	100.0%
ARIAD Pharmaceuticals, Inc.	U.S.	100.0%
Takeda Vaccines, Inc.	U.S.	100.0%
Takeda Development Center Americas, Inc.	U.S.	100.0%
Baxalta Incorporated	U.S.	100.0%
Dyax Corp.	U.S.	100.0%
Takeda Ventures, Inc.	U.S.	100.0%
Baxalta US Inc.	U.S.	100.0%
Shire Human Genetic Therapies, Inc.	U.S.	100.0%

Company name	Country	Ownership of Voting Rights (%)
Biolife Plasma Services LP	U.S.	100.0%
Takeda Manufacturing U.S.A., Inc.	U.S.	100.0%
Other 140 subsidiaries		

Associates accounted for using the equity method: 17 associates as of March 31, 2023

30. Related Party Transactions

Compensation for Key Management Personnel

Key management personnel are defined as members of the Board. The compensation for key management personnel is as follows:

	JPY (millions) For the Year Ended March 31		
	2021	2022	2023
Basic compensation and bonuses	¥ 1,664	¥ 1,614	¥ 1,640
Share-based compensation (expensed amount)	2,483	2,547	2,403
Other	42	38	43
Total	¥ 4,189	4,199	4,085

31. Business Combinations

Acquisitions during the Years ended March 31, 2021, 2022, and 2023

There was no material business combination during the years ended March 31, 2021, 2022, and 2023.

32. Commitments and Contingent Liabilities

Purchase commitments

The amount of contractual commitments for the acquisition of property, plant and equipment was 15,262 million JPY as of March 31, 2023.

Milestone Payments

As discussed in Note 13, Takeda has certain contractual agreements related to the acquisition of intangible assets that require it to make payments of up to 1,455,554 million JPY as of March 31, 2023. These commitments include development, regulatory approval and launch milestone payments in relation to R&D programs under development. The related commercial milestone payments were not included in the commitments given the payments were not deemed reasonably likely to occur.

Litigation

Takeda is involved in various legal and administrative proceedings. The most significant matters are described below.

Takeda may become involved in significant legal proceedings for which it is not possible to make a reliable estimate of the expected financial effect, if any, which may result from ultimate resolution of the proceedings. In these cases, appropriate disclosures about such cases would be included in this note, but no provision would be made for the cases.

With respect to each of the legal proceedings described below, other than those for which a provision has been made, Takeda is unable to make a reliable estimate of the expected financial effect at this stage. This is due to a number of factors, including, but not limited to, the stage of proceedings, the entitlement of parties to appeal a decision, if any, and lack of clarity as to the merits of theories of liability, the merits of Takeda's defenses, the amount and recoverability of damages and/or governing law. Takeda does not believe that information about the amount sought by the plaintiffs, if that is known, is, by itself, meaningful in every instance with respect to the outcome of those legal proceedings.

Legal expenses incurred and charges related to legal claims are recorded in selling, general and administrative expenses. Provisions are recorded, after taking appropriate legal and other specialist advice, where an outflow of resources is considered probable and a reliable estimate can be made of the likely outcome of the dispute. The factors Takeda considers in developing a provision include the merits and jurisdiction of the litigation, the nature and the number of other similar current and past litigation, the nature of the product and the current assessment of the science subject to the litigation, and the likelihood of settlement and current state of settlement discussions, if any. As of March 31, 2022 and 2023, Takeda's aggregate provisions for legal and other disputes were 42,869 million JPY and 64,290 million JPY, respectively. The ultimate liability for legal claims may vary from the amounts provided and is dependent upon the outcome of litigation proceedings, investigations and possible settlement negotiations. Unless otherwise stated below, Takeda is unable to predict the outcome or duration of these matters at this time.

Takeda's position could change over time, and, therefore, there can be no assurance that any losses that result from the outcome of any legal proceedings will not exceed, by a material amount, the amount of the provisions reported in these consolidated financial statements. Matters that were previously disclosed may no longer be reported because, as a result of rulings in the case, settlements, changes in our business or other developments, in our judgment, they are no longer material to our financial condition or operating results.

Product Liability and Related Claims

Pre-clinical and clinical trials are conducted during the development of potential products to determine the safety and efficacy of products for use by humans following approval by regulatory bodies. Notwithstanding these efforts, when drugs and vaccines are introduced into the marketplace, unanticipated safety issues may become, or be claimed by some to be, evident. Takeda is currently a defendant in a number of product liability lawsuits related to its products. For the product liability lawsuits and related claims, other than those for which a provision has been made, Takeda is unable to make a reliable estimate of the expected financial effect at this stage.

Takeda's principal pending legal and other proceedings are disclosed below. The outcomes of these proceedings are not always predictable and can be affected by various factors. For those legal and other proceedings for which it is considered at least reasonably possible that a loss has been incurred, Takeda discloses the possible loss or range of possible loss in excess of the recorded loss contingency provision, if any, where such excess is both material and estimable.

ACTOS

Economic Loss Cases

Takeda has been named in ACTOS-related lawsuits brought by plaintiffs who do not assert any claims for personal injuries. Instead plaintiffs claim they suffered an economic loss by paying for ACTOS prescriptions that allegedly would not have been written had Takeda provided additional information about the alleged risks of bladder cancer associated with ACTOS in its US product label. A putative class of third party payors and consumers brought suit against Takeda in the U.S. District Court for the Central District of California.

Proton Pump Inhibitor ("PPI") Product Liability Claims

As of March 31, 2023, more than 6,200 product liability lawsuits related to the use of PREVACID and DEXILANT have been filed against Takeda in U.S. federal and state courts. Most of these cases are pending in U.S. federal court and are consolidated for pre-trial proceedings in a multi-district litigation in federal court in New Jersey. The plaintiffs in these cases allege they developed kidney injuries or, in some cases, gastric cancer as a result of taking PREVACID and/or DEXILANT, and that Takeda failed to adequately warn them of these potential risks. Similar cases were filed against other manufacturers of drugs in the same PPI class as Takeda's products, including AstraZeneca plc ("AstraZeneca"), Procter & Gamble Company ("Procter & Gamble") and Pfizer Inc. ("Pfizer"). Outside the U.S., one proposed class action is pending in Canada (Saskatchewan). The defendants include Takeda, AstraZeneca, Janssen Pharmaceutical Companies ("Janssen") and several generic manufacturers.

Intellectual property

Intellectual property claims include challenges to the validity and enforceability of Takeda's patents on various products or processes as well as assertions of non-infringement of those patents. A loss in any of these cases could result in loss of patent protection for the product at issue. The consequences of any such loss could be a significant decrease in sales of that product and could materially affect future results of operations for Takeda.

TRINTELLIX

Takeda has received notices from sixteen generic pharmaceutical companies that they have submitted Abbreviated New Drug Applications ("ANDAs") with paragraph IV certifications seeking to sell generic versions of TRINTELLIX. Takeda filed patent infringement lawsuits against the ANDA filers in federal court in Delaware. Lawsuits against ten ANDA filers were resolved before trial. A trial took place from January 15 to January 28, 2021 with six ANDA filers, including Alembic Pharmaceuticals Limited and Alembic Pharmaceuticals, Inc., Lupin Limited and Lupin Pharmaceuticals, Inc. ("Lupin"), Macleods Pharmaceuticals Ltd., Sigmapharm Laboratories, LLC, Sandoz, Inc., and Zydus Pharmaceuticals (USA) Inc. and Cadila Healthcare Limited. The Court issued its decision on September 30, 2021 and found that US Patent 7,144,884, which covers vortioxetine (the active ingredient in Trintellix), is valid. For the rest of the asserted patent, only US Patent 9,101,626, which covers processes for synthesizing vortioxetine, was found to be infringed by Lupin. Takeda filed a notice of appeal on November 24, 2021. Lupin filed a notice of appeal on November 29, 2021 and other defendants filed a notice of appeal on December 8, 2021. The parties are awaiting scheduling of oral argument.

Other

In addition to the individual patent litigation cases described above, Takeda is party to a number of cases where Takeda has received notices that companies have submitted ANDAs with paragraph IV certifications to sell generic versions of other Takeda products. These include other Takeda products including Ponatinib. Takeda has filed patent infringement lawsuits against parties involved in these situations.

Sales, Marketing, and Regulation

Takeda has other litigations related to its products and its activities, the most significant of which are describe below.

ACTOS Antitrust Litigation

In December 2013, the first of two antitrust class action lawsuits was filed against Takeda in the U.S. District Court for the Southern District of New York by a putative class of patients who were prescribed ACTOS. The second class action was filed against Takeda in the same court in April 2015 by a putative class of wholesalers that purchased ACTOS from Takeda. In both actions, plaintiffs allege, inter alia, that Takeda improperly characterized certain patents for ACTOS in the FDA Orange Book, which they claim imposed requirements on generic companies that filed Abbreviated New Drug Applications and, in turn, resulted in delayed market entry for generic forms of ACTOS. In October 2019, the District Court denied Takeda's motion to dismiss. Takeda subsequently sought an interlocutory appeal of the District Court's decision, which was denied.

INTUNIV Antitrust Litigation

In January 2017, an antitrust class action was filed against Shire plc, Shire LLC, and Shire U.S. Inc. (collectively, "Shire") in the U.S. District Court for the District of Massachusetts. The plaintiffs, a putative class of wholesalers, allege that Shire's settlement in 2013 of patent litigation claims against Actavis Elizabeth LLC related to its generic formulation of INTUNIV constituted an anticompetitive "reverse payment."

AMITIZA Antitrust Litigation

In August 2021, an antitrust class action was filed against Takeda Pharmaceuticals U.S.A., Inc. ("Takeda") in the U.S. District Court for the District of Massachusetts. The plaintiffs, a putative class of wholesalers, allege that a settlement that Takeda and Sucampo Pharmaceuticals, Inc. entered into in 2014 with Par Pharmaceutical, Inc. ("Par") to resolve patent litigation claims related to Par's generic formulation of AMITIZA were anticompetitive.

COLCRYS Antitrust Litigation

In September 2021, an antitrust class action was filed against Takeda Pharmaceuticals U.S.A., Inc. ("Takeda") in the U.S. District Court for the Eastern District of Pennsylvania. The plaintiffs, a putative class of wholesalers, allege that settlements that Takeda entered into in 2015 and 2016 to resolve patent litigation claims against several generic drug manufacturers related to generic formulations of COLCRYS were anticompetitive.

AbbVie Supply Agreement Litigation

In November 2020, AbbVie brought suit against Takeda Pharmaceutical Company Limited ("Takeda") in Delaware Chancery Court alleging Takeda breached its agreement with AbbVie related to the supply of LUPRON in the U.S. due to shortages arising from quality issues the U.S. Food & Drug Administration identified concerning Takeda's production facility in Hikari, Japan as part of a Form 483 issued in November 2019 and a Warning Letter issued in June 2020. In the litigation, AbbVie sought both preliminary injunctive relief and monetary damages. In September 2021, the court issued an order denying AbbVie's request for injunctive relief. The court subsequently issued a decision finding Takeda in breach of the supply agreement. A trial to determine the amount of any damages was held in January 2023, and the court's decision is still pending.

Investigation of Patient Assistance Programs

In November 2016, the U.S. Department of Justice ("DOJ") (through the U.S. Attorneys' Office in Boston) issued a subpoena to Ariad Pharmaceuticals, Inc. ("Ariad"), which was acquired by Takeda during the year ended March 31, 2017, seeking information from January 2010 to the present relating to Ariad's donations to 501(c) (3) co-payment foundations, financial assistance programs, and free drug programs available to Medicare beneficiaries and the relationship between these co-payment foundations and specialty pharmacies, hubs or case management programs. Takeda is cooperating with the investigation.

In June 2019, the DOJ (through the U.S. Attorney's Office in Boston) issued a subpoena to Shire Pharmaceuticals LLC, which was acquired by Takeda during the year ended March 31, 2019 (through Takeda's acquisition of Shire plc). The subpoena generally seeks information about Shire's interactions with 501(c)(3) organizations that provide financial assistance to Medicare patients taking Shire drugs, including the hereditary angioedema medications FIRAZYR and CINRYZE. Takeda is cooperating with the investigation.

Department of Justice Civil Investigative Demands

On February 19, 2020, Takeda received a Civil Investigative Demand ("CID") from the DOJ (through its office in Washington, DC). The CID seeks information as part of an investigation of possible off-label promotion and violations of the Anti-kickback Statute in connection with the promotion and sale of TRINTELLIX. Takeda is cooperating with the DOJ's investigation.

On February 28, 2020, Takeda received a CID from the DOJ (through its office in Washington, DC). The CID seeks information as part of an investigation of possible kickbacks to a Florida allergy center in connection with the promotion and sale of Takeda's subcutaneous IG products, CUVITRU, HYQVIA and GAMMAGARD. Takeda is cooperating with the DOJ's investigation.

Brazilian Investigation Related to ELAPRASE and REPLAGAL

On November 30, 2021, the Brazilian federal authorities executed a search warrant at Takeda offices in Brazil. The warrant sought records about information Takeda received from the Brazilian National Sanitary Surveillance Agency (AVISA) as well as any records related to donations made to charitable organizations which provide funding to patients who are pursuing claims for reimbursement from the Brazilian government for prescriptions of ELAPRASE and REPLAGAL. Takeda is cooperating with the investigation.

33. Subsequent Events

On April 26, 2023, Takeda entered into new Syndicated Loans of 100 billion JPY with various banks maturing on April 26, 2030. The new Syndicated Loans have an effective interest rate of 0.68%. The proceeds from these Syndicated Loans were used to repay 100 billion JPY in existing Syndicated Loans falling due on the same day.

This is **Exhibit "1"** referred to in the Affidavit sworn remotely by Nick Boorman, stated as being at the City of Toronto, in the Province of Ontario, before me at the City of Toronto, in the Province of Ontario, on September 29, 2023, in accordance with O. Reg. 431/20, *Administering Oath or Declaration Remotely*

A Commissioner, etc.

Exhibit "2"

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2022

or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the transition period from to
Commission file number 001-36326

Endo International plc

(Exact name of registrant as specified in its charter)

Ireland	**68-0683755**
State or other jurisdiction of incorporation or organization	(I R S Employer Identification No)
First Floor, Minerva House, Simmonscourt Road **Ballsbridge, Dublin 4, Ireland**	**Not Applicable**
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code: **011-353-1-268-2000**

Securities registered pursuant to Section 12(b) of the Act: None (1)

(1) On August 26, 2022, Endo International plc's ordinary shares, which previously traded on the Nasdaq Global Select Market under the symbol ENDP, began trading exclusively on the over-the-counter market under the symbol ENDPQ. On September 14, 2022, Nasdaq filed a Form 25-NSE with the United States Securities and Exchange Commission and Endo International plc's ordinary shares were subsequently delisted from the Nasdaq Global Select Market. On December 13, 2022, Endo International plc's ordinary shares were deregistered under Section 12(b) of the Securities Exchange Act of 1934, as amended.

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act	Yes	☐	No	☒
Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act	Yes	☐	No	☒
Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days	Yes	☒	No	☐
Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232 405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files)	Yes	☒	No	☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act

Large accelerated filer	☐	Accelerated filer	☒
Non-accelerated filer	☐	Smaller reporting company	☒
		Emerging growth company	☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act	☐
Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U S C 7262(b)) by the registered public accounting firm that prepared or issued its audit report	☒
If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements	☐
Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to § 240 10D-1(b)	☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act)	Yes	☐	No	☒

The aggregate market value of the voting common equity (ordinary shares) held by non-affiliates as of June 30, 2022 (the last business day of the registrant's most recently completed second fiscal quarter) was $109,653,452 based on a closing sale price of $0 47 per share as reported on The Nasdaq Global Select Market on that date Ordinary shares held by each officer and director have been excluded since such persons and beneficial owners may be deemed to be affiliates This determination of affiliate status is not necessarily a conclusive determination for other purposes The registrant has no non-voting ordinary shares authorized or outstanding

The number of ordinary shares, nominal value $0 0001 per share outstanding as of February 27, 2023 was 235,219,612

ENDO INTERNATIONAL PLC
(DEBTOR-IN-POSSESSION)
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FOR THE YEAR ENDED DECEMBER 31, 2022

FORWARD-LOOKING STATEMENTS

Statements contained or incorporated by reference in this document contain information that includes or is based on "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, as amended (Securities Act) and Section 21E of the Securities Exchange Act of 1934, as amended (Exchange Act) and the Private Securities Litigation Reform Act of 1995. Forward-looking statements include, without limitation, any statements relating to future financial re ult , co t avin , revenue , expen e , net income and income per hare; the tatu , pro re and/or outcome of litigation, proceedings under chapter 11 of title 11 of the United States (U.S.) Code (the Bankruptcy Code) and/or any other contingency planning initiatives, including the application and effect of the automatic stay thereunder; future financing activities; the impact of COVID-19 on the health and welfare of our employees and on our business (including any economic impact, anticipated return to historical purchasing decisions by customers, changes in consumer spending, decisions to engage in certain medical procedures, future governmental orders that could impact our operations and the ability of our manufacturing facilitie and upplier to fulfill their obligation to u); the expan ion of our product pipeline and any development, approval, launch or commercialization activities; and any other statements that refer to Endo's expected, estimated or anticipated future results. We have tried, whenever possible, to identify such statements with words such as "believe," "expect," "anticipate," "intend," "estimate," "plan," "project," "forecast," "will," "may" or similar expressions. We have based these forward-looking statements on our current expectations, assumptions and projections about, among other things, the growth of our business, our financial performance and the development of our industry.

Because these statements reflect our current views concerning future events, these forward-looking statements involve risks and uncertainties including, without limitation, the timing or results of any pending or future litigation, investigations, claims, actual or contingent liabilities, settlement di cu ion , ne otiation or other adver e proceedin , includin proceedin involving opioid related matter , antitru t matter and tax matter with the U.S. Internal Revenue Service (IRS); unfavorable publicity regarding the misuse of opioids; the status, progress and/or outcome of our ongoing bankruptcy proceedings; changing competitive, market and regulatory conditions; changes in legislation; our ability to obtain and maintain adequate protection for our intellectual property rights; the impacts of competition such as those related to the loss of VASOSTRICT® exclusivity; the timing and uncertainty of the results of both the research and development and regulatory processes, including regulatory decisions, product recalls, withdrawals and other unusual items; domestic and foreign health care and cost containment reforms, including government pricing, tax and reimbursement policies; technological advances and patents obtained by competitors; the performance, including the approval, introduction and consumer and physician acceptance of new products and the continuing acceptance of currently marketed products; our ability to develop or expand our product pipeline and to continue to develop the market for XIAFLEX® and other branded or unbranded products; the impact that known and unknown side effects may have on market perception and consumer preference; the success of any acquisition, licensing or commercialization; the effectiveness of advertising and other promotional campaigns; the timely and successful implementation of any strategic and/or optimization initiatives; the uncertainty associated with the identification of and successful consummation and execution of external corporate development initiatives and strategic partnering transactions; our ability to obtain and successfully manufacture, maintain and distribute a sufficient supply of products to meet market demand in a timely manner; and the other risks and uncertainties more fully described under the caption "Risk Factors" in Part I, Item 1A of this Annual Report on Form 10-K and in other reports that we file with the Securities and Exchange Commission (SEC).

These risks and uncertainties, many of which are outside of our control, and any other risks and uncertainties that we are not currently able to predict or identify, individually or in the aggregate, could have a material adverse effect on our business, financial condition, results of operations and cash flows and could cause our actual results to differ materially and adversely from those expressed in forward-looking statements contained or referenced in this document, including with respect to opioid, tax or antitrust related proceedings or any other litigation; the effects of our ongoing bankruptcy proceedings and the related events of default under our indebtedness on our current and future liquidity and ability to fund our working capital, capital expenditures, business development, debt service requirements, acquisitions and any other obligations; our ability to attract and retain key personnel; our ability to adjust to changing market conditions; and/or the potential for a significant reduction in our short-term and long-term revenues and/or any other factor that could cause us to be unable to fund our operations and liquidity needs.

We do not undertake any obligation to update our forward-looking statements after the date of this document for any reason, even if new information becomes available or other events occur in the future, except as may be required under applicable securities laws. You are advised to consult any further disclosures we make on related subjects in our reports filed with the SEC and with securities regulators in Canada on the System for Electronic Document Analysis and Retrieval (SEDAR). Also note that, in Part I, Item 1A, we provide a cautionary discussion of risks, uncertainties and possibly inaccurate assumptions relevant to our business. These are factors that, individually or in the aggregate, we think could cause our actual results to differ materially from expected and historical results. We note these factors for investors as permitted by Section 27A of the Securities Act and Section 21E of the Exchange Act. You should understand that it is not possible to predict or identify all such factors. Consequently, you should not consider this to be a complete discussion of all potential risks or uncertainties.

PART I

Item 1. *Business*

Overview

Unless otherwise indicated or required by the context, references throughout to "Endo," the "Company," "we," "our" or "us" refer to Endo International plc and its subsidiaries.

Endo International plc is an Ireland-domiciled specialty pharmaceutical company. Endo International plc was incorporated in Ireland in 2013 as a private limited company and re-registered effective February 18, 2014 as a public limited company. Endo International plc is a holding company that conducts business through its operating subsidiaries.

Our ordinary shares, which previously traded on the Nasdaq Global Select Market under the ticker symbol "ENDP," are currently quoted on the over-the-counter market using the ticker symbol "ENDPQ." References throughout to "ordinary shares" refer to Endo International plc's ordinary shares (1,000,000,000 authorized, par value of $0.0001 per share). In addition, we have 4,000,000 euro deferred shares outstanding (par value of $0.01 per share).

The address of Endo International plc's headquarters is Minerva House, Simmonscourt Road, Ballsbridge, Dublin 4, Ireland (telephone number: 011-353-1-268-2000).

Our focus is on pharmaceutical products and we target areas where we believe we can build leading positions. Our operating model is based on a lean and nimble structure, the rational allocation of capital and an emphasis on high-value research and development (R&D) targets. While our primary focus is on organic growth, we evaluate and, where appropriate, execute on opportunities to expand through the licensing or acquisition of products or companies in areas that we believe serve patients and customers while offering attractive growth characteristics and margins. We believe our operating model and the execution of our corporate strategy will enable us to create shareholder value over the long-term.

The four reportable business segments in which we operate are: (1) Branded Pharmaceuticals, (2) Sterile Injectables, (3) Generic Pharmaceuticals and (4) International Pharmaceuticals. Additional information about our reportable business segments is included throughout this Part I. The results of operations of our reportable business segments are discussed in Part II, Item 7 of this report "Management's Discussion and Analysis of Financial Condition and Results of Operations" under the heading "RESULTS OF OPERATIONS." Across all of our reportable business segments, we generated total revenues of $2.32 billion, $2.99 billion and $2.90 billion in 2022, 2021 and 2020, respectively.

For branded products, which we sell primarily through our Branded Pharmaceuticals and Sterile Injectables segments, we seek to invest in products or product candidates that have inherent scientific, regulatory, legal and technical complexities and market such products under recognizable brand names that are trademarked. For products we develop for the U.S. market, after the completion of required clinical trials and testing, we seek approvals from regulatory bodies such as through the submission of New Drug Applications (NDAs) or Biologics License Applications (BLAs) to the U.S. Food and Drug Administration (FDA). We believe that our patents, the protection of discoveries in connection with our development activities, our proprietary products, technologies, processes, trade secrets, know-how, innovations and all of our intellectual property are important to our business and achieving a competitive position. However, there can be no assurance that any of our patents, licenses or other intellectual property rights will afford us any protection from competition. Additional information is included throughout this Part I, Item 1.

Generic products are the pharmaceutical and therapeutic equivalents of branded products and are generally sold under their generic (chemical) names rather than their brand names. For generic products, which we sell primarily through our Sterile Injectables and Generic Pharmaceuticals segments, our focus is on high-barrier-to-entry products, with an emphasis on complex sterile injectable products, such as ready-to-use (RTU) products, and first-to-file or first-to-market opportunities that are difficult to formulate or manufacture or face complex legal and regulatory challenges. In the U.S., first-to-file products refer to generic products for which the Abbreviated New Drug Applications (ANDAs) containing patent challenges (or Paragraph IV certifications) to the corresponding branded products' listed patents were the first to be filed with the FDA. In the U.S., manufacturers that launch first-to-file products, after success in litigating or otherwise resolving related patent challenges, and receive final FDA approval have the opportunity for 180 days of generic marketing exclusivity from competing generic products other than authorized generics. First-to-market products refer to products that are the first marketed generic equivalents of the corresponding branded products for reasons apart from statutory marketing exclusivity. This can occur, for example, when a generic product is difficult to formulate or manufacture. First-to-market products allow manufacturers to mitigate risks from competitive pressures commonly associated with commoditized generic products. Additional information is included throughout this Part I, Item 1.

Bankruptcy Proceedings

On August 16, 2022 (the Petition Date), Endo International plc, together with certain of its direct and indirect subsidiaries (the Debtors), filed voluntary petitions for relief under the Bankruptcy Code, which constituted an event of default that accelerated our obligations under substantially all of our then-outstanding debt instruments. However, section 362 of the Bankruptcy Code stays creditors from taking any action to enforce the related financial obligations and creditors' rights of enforcement in respect of the debt instruments are subject to the applicable provisions of the Bankruptcy Code. As a result of these conditions and events, management continues to believe there is substantial doubt about our ability to continue as a going concern within one year after the date of issuance of the Consolidated Financial Statements included in Part IV, Item 15 of this report. Additional information regarding our ongoing bankruptcy proceedings is included throughout this report including, without limitation, information about recent and potential future developments related to our bankruptcy proceedings and certain related transactions, the effects of our ongoing bankruptcy proceedings and certain related transactions on our business and financial statements to date and the potential future effects of such proceedings and transactions, including discussions of related risks and uncertainties.

Our Strategy

Endo International plc is a specialty pharmaceutical company committed to helping everyone we serve live their best life through the delivery of high-quality, life-enhancing therapies. We are focused on driving long-term growth through a diversified and durable portfolio of businesses, continuing product development and manufacturing and commercialization excellence. Our strategic priorities include expanding and enhancing our portfolio with differentiated and durable products; reinventing how we work to better serve our customers, promote innovation and improve productivity; and being a force for good by embracing and adopting sustainable practices that benefit all of our stakeholders. Specific areas of management's focus include:

- Branded Pharmaceuticals: Accelerating performance of organic growth drivers in our Specialty Products portfolio and expanding margin in our Established Products portfolio. As further described below under the heading "Select Development Projects," management is also focused on investing in key product life cycle management and other development opportunities, with a focus on non-surgical orthopedic care interventions.
- Sterile Injectables: Focusing on developing injectable products with inherent scientific, regulatory, legal and technical complexities, expanding the product portfolio to include other dosages and technologies and developing or acquiring high-barrier-to-entry products that are difficult to manufacture.
- Generic Pharmaceuticals: Focusing on developing or acquiring high-barrier-to-entry products, including first-to-file or first-to-market opportunities that are difficult to formulate or manufacture or face complex legal and regulatory challenges.

Additionally, as part of our Environmental, Social and Governance (ESG) strategy, we are committed to the adoption of more sustainable practices, including the promotion of Diversity, Equity and Inclusion (DE&I) in all that we do, and to operating our business in a responsible manner that seeks to minimize environmental impact, while promoting the safe, efficient and responsible use of global resources.

While our primary focus is on organic growth, we plan to continue to evaluate and, where appropriate, execute on opportunities to expand through the licensing or acquisition of products or companies. There can be no assurance that we will be successful in executing on our strategy.

Our Competitive Strengths

To successfully execute our strategy, we must continue to capitalize on our following core strengths:

Experienced and dedicated management team. We have a highly skilled and customer-focused management team in critical leadership positions across Endo. Our senior management team has extensive experience in the pharmaceutical industry, including improving business performance through organic revenue growth, operational and commercial excellence and through the identification, consummation and integration of licensing and acquisition opportunities. This experience is demonstrated through a proven track record of developing products and businesses.

Operational excellence. We have efficient, high-quality manufacturing capabilities across a diversified array of dosage forms in the U.S. and India. We believe our comprehensive suite of technology, manufacturing and development competencies increases the likelihood of success in commercializing high-barrier-to-entry products and obtaining first-to-file and first-to-market status on future products, yielding more sustainable market share and profitability. For example, our expanding capabilities in the rapidly growing U.S. market for sterile products afford us with a broader and more diversified product portfolio and a greater selection of targets for potential development.

We believe that our competitive advantages include our integrated team-based approach to product development that combines our global formulation, regulatory, legal, manufacturing and commercial capabilities; our ability to introduce new generic equivalents for brand-name products; our quality and cost-effective production; our ability to meet customer and/or patient expectations and the breadth of our existing product offerings.

Growth of our branded Specialty Products portfolio while leveraging the strength of our Established Products portfolio. We have assembled a portfolio of branded products offered by our Branded Pharmaceuticals segment in the areas of urology, orthopedics, endocrinology and bariatrics, among others. Additional information on these product portfolios is included below under the heading "Products Overview."

Optimizing our portfolios to focus on differentiated products. By leveraging operational efficiency and taking actions to optimize our cost structure when appropriate, we aim to be low-cost producers of high-barrier-to-entry products, including products that meet the evolving needs of hospitals and health systems, including RTU sterile injectable products, and first-to-file and first-to-market generic opportunities that are difficult to formulate or manufacture or face complex legal and regulatory challenges. We believe that focusing on products with these characteristics will result in products with longer life cycles and higher profitability than products without these characteristics.

Continuing proactive diversification of our business. Our primary focus is on organic growth. However, we plan to continue to evaluate and, where appropriate, execute on opportunities to expand through the licensing or acquisition of products or companies in areas that will serve patients and customers and that we believe will offer attractive growth characteristics and margins. In particular, we intend to continue to enhance our product lines by acquiring or licensing rights to additional products and regularly evaluating selective acquisition opportunities.

R&D expertise. Our R&D efforts are focused on the development of a diversified portfolio of innovative and clinically differentiated product candidates. For example, in recent years, our Branded Pharmaceuticals research has focused on leveraging our expertise in collagenase clostridium histolyticum (CCH) and seeking additional novel indications for this class of biologics. Our Sterile Injectables and Generic Pharmaceuticals segments seek out and develop high-barrier-to-entry products, with an emphasis on complex sterile injectable products, such as RTU products, and first-to-file or first-to-market opportunities. We periodically review our R&D pipeline in order to better direct investment toward those opportunities that we expect will deliver the greatest returns. Our current R&D pipeline consists of products in various stages of development and reflects our expanded focus on Sterile Injectables products and solutions. For additional detail, see "Select Development Projects." Our R&D and regulatory affairs staff is based primarily in India and the U.S.

Targeted sales and marketing capabilities. Our sales and marketing activities are based in the U.S. and Canada and primarily focus on the promotion of our Specialty Products portfolio and Sterile Injectables segment.

We market our Specialty Products directly to specialty physicians, including those specializing in urology, orthopedics, pediatric endocrinology and bariatric surgery. Our sales force also directs its marketing efforts on retail pharmacies and other healthcare professionals. We distribute our Specialty Products through independent wholesale distributors, but we also sell directly to retailers, clinics, government agencies, doctors, independent retail and specialty pharmacies and independent specialty distributors. Our marketing policy is designed to provide physicians, pharmacies, hospitals, public and private payers and appropriate healthcare professionals with products and appropriate medical information. We work to gain access to various formularies (lists of recommended or approved medicines and other products) and reimbursement lists by demonstrating the qualities and treatment benefits of our products within their approved indications.

In addition to advertising in professional journals, participating in medical meetings and conventions and utilizing direct mail and internet programs to provide descriptive product literature and scientific information, we have also utilized both branded and unbranded marketing and public relations campaigns across digital, social and television platforms to reach our target consumers. For example, during the first quarter of 2022, we launched a new Dupuytren's contracture (DC) condition awareness campaign featuring real patients and, during the fourth quarter of 2021, we launched a new multi-channel branded advertising campaign for XIAFLEX® for the treatment of Peyronie's disease (PD), including our first-ever television commercial for XIAFLEX®.

Our dedicated Sterile Injectables sales and marketing team is focused on health systems and national group purchasing organizations (GPOs). Our customers' growing complexity requires us to engage directly with key stakeholders and decision makers. Our experienced sales and marketing team is key to growing our existing portfolio and executing on new product launches.

Products Overview

Branded Pharmaceuticals

The following table displays the revenues from external customers of our Branded Pharmaceuticals segment for the years ended December 31, 2022, 2021 and 2020 (in thousands):

	2022	2021	2020
Specialty Products:			
XIAFLEX®	$ 438,680	$ 432,344	$ 316,234
SUPPRELIN® LA	113,011	114,374	88,182
Other Specialty (1)	70,009	86,432	92,662
Total Specialty Products	$ 621,700	$ 633,150	$ 497,078
Established Products:			
PERCOCET®	$ 103,943	$ 103,788	$ 110,112
TESTOPEL®	38,727	43,636	35,234
Other Established (2)	86,772	113,043	139,356
Total Established Products	$ 229,442	$ 260,467	$ 284,702
Total Branded Pharmaceuticals (3)	$ 851,142	$ 893,617	$ 781,780

(1) Products included within Other Specialty include AVEED®, NASCOBAL® Nasal Spray and QWO®
(2) Products included within Other Established include, but are not limited to, EDEX®
(3) Individual products presented above represent the top two performing products in each product category for the year ended December 31, 2022 and/or any product having revenues in excess of $25 million during any completed quarterly period in 2022 or 2021

Specialty Products Portfolio

Endo commercializes a number of products within the market served by specialty distributors and specialty pharmacies and in which healthcare practitioners can purchase and bill payers directly (the buy and bill market). Our current offerings primarily relate to the following areas: (i) urology treatments, which currently focus mainly on PD and testosterone replacement therapies (TRT) for hypogonadism; (ii) orthopedics treatments, which currently focus on DC; and (iii) pediatric endocrinology treatments, which currently focus on central precocious puberty (CPP). Key product offerings in this portfolio include the following:

- XIAFLEX®, which is a non-surgical treatment for both DC (for adult patients with an abnormal buildup of collagen in the fingers that limits or disables hand function) and PD (for adult men with a collagen plaque and a penile curvature deformity of thirty degrees or greater at the start of therapy).
- SUPPRELIN® LA, which is a soft, flexible 12-month hydrogel implant based on our hydrogel polymer technology that delivers histrelin acetate, a gonadotropin-releasing hormone agonist, and is indicated for the treatment of CPP in children.
- AVEED®, which is a novel, long-acting testosterone undecanoate for injection for the treatment of hypogonadism that is dosed only five times per year after the first month of therapy.
- NASCOBAL® Nasal Spray, which is a prescription nasal spray used as a supplement to treat vitamin B12 deficiency.

This portfolio has also included QWO® (collagenase clostridium histolyticum-aaes), an injectable treatment for moderate to severe cellulite in the buttocks of adult women launched in March 2021. However, in December 2022, the Company announced it would be ceasing the production and sale of QWO® in light of market concerns about the extent and variability of bruising following initial treatment as well as the potential for prolonged skin discoloration.

Established Products Portfolio

This portfolio's current treatment offerings primarily relate to the following areas: (i) pain management, including products in the opioid analgesics segment and for the treatment of pain associated with post-herpetic neuralgia, and (ii) urology, focusing mainly on the treatment of hypogonadism. Key product offerings in this portfolio include, among others, the following:

- PERCOCET®, which is an opioid analgesic approved for the treatment of moderate to moderately-severe pain.
- TESTOPEL®, which is a unique, long-acting implantable pellet indicated for TRT in conditions associated with a deficiency or absence of endogenous testosterone.
- EDEX®, which is a penile injection used to treat erectile dysfunction caused by conditions affecting nerves, blood vessels, emotions and/or a combination of factors.

The Company's pain products, including opioid products, are managed as mature brands and are not and have not been actively promoted for years. In December 2016, the Company announced the elimination of its entire U.S. pain product field sales force.

Sterile Injectables

The following table displays the revenues from external customers of our Sterile Injectables segment for the years ended December 31, 2022, 2021 and 2020 (in thousands):

	2022	2021	2020
VASOSTRICT®	$ 253,696	$ 901,735	$ 785,646
ADRENALIN®	114,304	124,630	152,074
Other Sterile Injectables (1)	221,633	239,732	301,127
Total Sterile Injectables (2)	$ 589,633	$ 1,266,097	$ 1,238,847

(1) Products included within Other Sterile Injectables include APLISOL®, ertapenem for injection and others
(2) Individual products presented above represent the top two performing products within the Sterile Injectables segment for the year ended December 31, 2022 and/or any product having revenues in excess of $25 million during any completed quarterly period in 2022 or 2021

The Sterile Injectables segment includes a product portfolio of approximately 40 product families, including branded sterile injectable products that are currently protected by certain patent rights and have inherent scientific, regulatory, legal and technical complexities and generic injectable products that are difficult to formulate or manufacture or face complex legal and regulatory challenges. Our sterile injectables products are manufactured in sterile facilities in various dosage forms and are administered at hospitals, clinics and long-term care facilities. Key product offerings in this segment include, among others, the following:

- VASOSTRICT®, which is indicated to increase blood pressure in adults with vasodilatory shock who remain hypotensive despite fluids and catecholamines. We offer VASOSTRICT® in multiple formulations, including the RTU pre-mix bottle we launched in February 2022.
- ADRENALIN®, which is a non-selective alpha and beta adrenergic agonist indicated for emergency treatment of certain allergic reactions, including anaphylaxis.
- APLISOL®, which is a sterile aqueous solution of a purified protein derivative for intradermal administration as an aid in the diagnosis of tuberculosis.
- Ertapenem for injection (the authorized generic of Merck Sharp & Dohme Corp.'s (Merck) Invanz®), which is indicated for the treatment of certain moderate to severe infections.
- Ephedrine sulfate injection, which is an alpha and beta adrenergic agonist and a norepinephrine-releasing agent indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia.

Generic Pharmaceuticals

The Generic Pharmaceuticals segment includes a product portfolio of approximately 110 generic product families including solid oral extended-release products, solid oral immediate-release products, liquids, semi-solids, patches (which are medicated adhesive patches designed to deliver the pharmaceutical through the skin), powders, ophthalmics (which are sterile pharmaceutical preparations administered for ocular conditions) and sprays and includes products that treat and manage a wide variety of medical conditions.

Generic products are the pharmaceutical and therapeutic equivalents of branded products and are generally sold under their generic (chemical) names rather than their brand names. Generic products are substantially the same as branded products in dosage form, safety, efficacy, route of administration, quality, performance characteristics and intended use, but are generally sold at prices below those of the corresponding branded products and thus represent cost-effective alternatives for consumers.

Typically, a generic product may not be marketed until the expiration of applicable patent(s) on the corresponding branded product unless a resolution of patent litigation results in an earlier opportunity to enter the market. For additional detail, see "Governmental Regulation." However, our generics portfolio also contains certain authorized generics, which are generic versions of branded products licensed by brand drug companies under an NDA and marketed as generics. Authorized generics do not face the same regulatory barriers to introduction and are not prohibited from sale during the 180-day marketing exclusivity period granted to the first-to-file ANDA applicant. From time to time, our authorized generics have included generic versions of our branded products. We also aim to be a partner of choice to large companies seeking authorized generic distributors for their branded products. For example, in January 2021, we launched lubiprostone capsules (the authorized generic of Mallinckrodt plc's Amitiza®).

International Pharmaceuticals

Our International Pharmaceuticals segment includes a variety of specialty pharmaceutical products, including over-the-counter (OTC) products, sold outside the U.S., primarily in Canada through our operating company Paladin Labs Inc. (Paladin).

Select Development Projects

XIAFLEX®

XIAFLEX® is currently approved by the FDA and marketed in the U.S. for the treatment of both DC and PD (two separate indications). In early 2020, we announced that we had initiated our XIAFLEX® development program for the treatment of plantar fibromatosis, for which we anticipate Phase 2 top-line data by the end of the first quarter of 2023. We also initiated a proof-of-concept study in plantar fasciitis during the fourth quarter of 2022. We may in the future develop our XIAFLEX® product for potential additional indications, advancing our strategy of developing non-surgical orthopedic care interventions.

As further described in Note 12. License, Collaboration and Asset Acquisition Agreements in the Consolidated Financial Statements included in Part IV, Item 15 of this report, we completed our acquisition of BioSpecifics Technologies Corp., a Delaware corporation and a commercial-stage biopharmaceutical company (BioSpecifics) in December 2020. Prior to this acquisition, we had a strategic relationship with BioSpecifics since 2004 pursuant to which BioSpecifics was, among other things, entitled to a royalty stream from us related to our collagenase-based therapies, including XIAFLEX®. Subsequent to the acquisition, BioSpecifics became our wholly-owned consolidated subsidiary.

TLC599

In June 2022, we announced that our subsidiary had entered into an agreement with Taiwan Liposome Company, Ltd. (TLC) to commercialize TLC599. TLC599 is an injectable compound in Phase 3 development for the treatment of osteoarthritis knee pain.

In September 2022, we were informed by TLC of the top-line results from TLC's Phase 3 clinical study to evaluate the efficacy and safety of TLC599 in patients with pain from osteoarthritis of the knee. While study participants treated with TLC599 showed improvement on the primary endpoint (change from baseline to week 12 on the WOMAC pain scale) consistent with the level of improvement reported in the previously conducted TLC599 Phase 2 clinical study, the difference compared to those receiving placebo was not statistically significant. Based on these data, we are evaluating options for TLC599 with TLC.

Other

Our remaining pipeline consists mainly of a variety of product candidates in our Sterile Injectables and Generic Pharmaceuticals segments. As of December 31, 2022, within these two segments, we were actively pursuing approximately 70 product candidates, including: (i) approximately 30 ANDAs pending with the FDA, of which approximately 40% are associated with our Sterile Injectables segment, as well as (ii) approximately 40 additional projects in development, of which approximately 90% are associated with our Sterile Injectables segment, including RTU and other more differentiated product candidates.

We expect to continue to focus investments in RTU and other product candidates in our Sterile Injectables segment, potentially including acquisitions and/or license and commercialization agreements such as the 2022 Nevakar Agreement that is further described in Note 12. License, Collaboration and Asset Acquisition Agreements in the Consolidated Financial Statements included in Part IV, Item 15 of this report.

Our primary approach to developing generic products for these two segments is to target high-barrier-to-entry product opportunities, including first-to-file or first-to-market opportunities that are difficult to formulate or manufacture or face complex legal and regulatory challenges as well as products that meet the evolving needs of hospitals and health systems. We expect such product opportunities to result in products that are either the exclusive generic or have two or fewer generic competitors when launched, which we believe tends to lead to more sustainable market share and profitability for our product portfolio. In our Sterile Injectables business, we also focus on developing injectable products with inherent scientific, regulatory, legal and technical complexities, as well as developing other dosage forms and technologies.

We periodically review our development projects in order to better direct investment toward those opportunities that we expect will deliver the greatest returns. This process can lead to decisions to discontinue certain R&D projects that may reduce the number of products in our previously reported pipeline.

Major Customers

We primarily sell our products to wholesalers, retail drug store chains, supermarket chains, mass merchandisers, distributors, mail order accounts, hospitals and/or government agencies. Our wholesalers and/or distributors purchase products from us and, in turn, supply products to retail drug store chains, independent pharmacies, hospitals, long-term care facilities, clinics, home infusion pharmacies, government facilities and managed care organizations (MCOs). Our current customer group reflects significant consolidation in recent years, marked by mergers and acquisitions and other alliances. Net revenues from direct customers that accounted for 10% or more of our total consolidated net revenues during the years ended December 31, 2022, 2021 and 2020 are as follows:

	2022	2021	2020
AmerisourceBergen Corporation	35 %	36 %	33 %
McKesson Corporation	26 %	32 %	27 %
Cardinal Health, Inc.	20 %	22 %	24 %

Revenues from these customers are included within each of our segments.

Some wholesalers and distributors have required pharmaceutical manufacturers, including us, to enter into distribution service agreements (DSAs) pursuant to which the wholesalers and distributors provide pharmaceutical manufacturers with certain services as well as certain information including, without limitation, periodic retail demand information, current inventory levels and other information. We have entered into certain of these agreements.

Competition

Branded Products

Our branded products compete with products manufactured by many other companies in highly competitive markets.

We compete principally through targeted product development and through our acquisition and in-licensing strategies, where we face intense competition as a result of the limited number of assets available and the number of competitors bidding on such assets. In addition to product development and acquisitions, other competitive factors with respect to branded products include product efficacy, safety, ease of use, price, demonstrated cost-effectiveness, marketing effectiveness, service, reputation and access to technical information.

Branded products often must compete with therapeutically similar branded or generic products or with generic equivalents. Such competition frequently increases over time. For example, if competitors introduce new products, delivery systems or processes with therapeutic or cost advantages, our products could be subject to progressive price reductions and/or decreased volume of sales. To successfully compete for business, we must often demonstrate that our products offer not only medical benefits, but also cost advantages as compared with other forms of care. Accordingly, we face pressure to continually seek out technological innovations and to market our products effectively.

Manufacturers of generic products typically invest far less in R&D than research-based companies and can therefore price their products significantly lower than branded products. Accordingly, when a branded product loses its market exclusivity, it normally faces intense price competition from generic forms of the product. Due to lower prices, generic versions, where available, may be substituted by pharmacies or required in preference to branded versions under third-party reimbursement programs.

Branded Pharmaceuticals

This segment’s major competitors, including Viatris Inc. (Viatris), Jazz Pharmaceuticals plc, Takeda Pharmaceutical Company Limited and Horizon Therapeutics Public Limited Company, among others, vary depending on therapeutic and product category, dosage strength and drug-delivery systems, among other factors.

Several of this segment’s products, such as PERCOCET®, TESTOPEL® and SUPPRELIN® LA, face generic and/or other forms of competition. The degree of generic and/or other competition facing this segment could increase in the future.

Sterile Injectables

This segment’s major competitors, including Hospira, Inc. (a subsidiary of Pfizer Inc.), Fresenius Kabi USA, LLC, Viatris, Amphastar Pharmaceuticals, Inc., Amneal Pharmaceuticals, Inc. (Amneal), Hikma Pharmaceuticals PLC, Sandoz and Eagle Pharmaceuticals, Inc. (Eagle), among others, vary by product. A significant portion of our sales, including sales to hospitals, clinics and long-term care facilities in the U.S., are controlled by a relatively small number of GPOs, including HealthTrust Purchasing Group, L.P., Premier Inc. and Vizient, Inc. Accordingly, it is important for us to have strong relationships with these GPOs and achieve on-time product launches in order to secure new bid opportunities.

This segment's products, including VASOSTRICT® and ADRENALIN®, face generic and/or other forms of competition. During the first quarter of 2022, multiple competitive generic alternatives to VASOSTRICT® were launched, beginning with a generic that was launched at risk and began shipping toward the end of January 2022. Since then, additional competitive alternatives entered the market, including authorized generics. The degree of generic and/or other competition facing this segment is expected to increase in the future.

Generic Products

Generic products generally face intense competition from branded equivalents, other generic equivalents (including authorized generics) and therapeutically similar branded or generic products. Our major competitors, including Teva Pharmaceutical Industries Limited, Viatris, Sandoz, Aurobindo Pharma Limited and Amneal, among others, vary by product.

Consolidations of our customer base described above under the heading "Major Customers" have resulted in increased pricing and other competitive pressures on pharmaceutical companies, including us. Additionally, the emergence of large buying groups representing independent retail pharmacies and other distributors and the prevalence and influence of MCOs and similar institutions have increased the negotiating power of these groups, enabling them to attempt to extract various demands, including without limitation price discounts, rebates and other restrictive pricing terms. These competitive trends could continue in the future and could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Newly introduced generic products with limited or no other generic competition typically garner higher prices relative to commoditized generic products. As such, our primary strategy is to compete with a focus on high-value, first-to-file or first-to-market opportunities, regardless of therapeutic category, and products that present significant barriers to entry for reasons such as complex formulation or regulatory or legal challenges. For additional detail, see "Our Competitive Strengths - Optimizing our portfolios to focus on differentiated products."

Even if we are successful in launching generic products with statutory generic exclusivity, competitors may enter the market when such exclusivity periods expire, resulting in significant price declines. Consequently, the success of our generics efforts depends on our continuing ability to select, develop, procure regulatory approvals of, overcome legal challenges to, launch and commercialize new generic products in a timely and cost efficient manner and to maintain efficient, high quality manufacturing capabilities. For additional detail, see "Our Competitive Strengths - Operational excellence."

Seasonality

Although our business is affected by the purchasing patterns and concentration of our customers, our business is not materially impacted by seasonality.

Patents, Trademarks, Licenses and Proprietary Property

We regard the protection of patents and other enforceable intellectual property rights that we own or license as critical to our business and competitive position. Accordingly, we rely on patent, trade secret and copyright law, as well as nondisclosure and other contractual arrangements, to protect our intellectual property. We have a portfolio of patents and patent applications owned or licensed by us that cover aspects of our products. These patents and applications generally include claims directed to the compounds and/or methods of using the compounds, formulations of the compounds, pharmaceutical salt forms of the compounds or methods of manufacturing the compounds. Our policy is to pursue patent applications on inventions that we believe are commercially important to the development and growth of our business.

Certain patents relating to products that are the subject of approved NDAs are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book). The Orange Book does not include a listing of patents related to biological products approved pursuant to a BLA. Included below is information about certain products for which we own or license a BLA along with the date of expiration of certain relevant patents or regulatory exclusivity. In addition, we may have other relevant regulatory protection or patents that may extend beyond the expiration dates provided below.

As of February 27, 2023, we held approximately: 152 U.S. issued patents, 45 U.S. patent applications pending, 427 foreign issued patents and 119 foreign patent applications pending. In addition, as of February 27, 2023, we had licenses for approximately 73 U.S. issued patents, 14 U.S. patent applications pending, 167 foreign issued patents and 83 foreign patent applications pending. We are seeking additional patent protection for several products, including XIAFLEX®. We may also obtain further patents or additional regulatory or patent exclusivity for one or more indications for any of our products in the future.

Our products are subject to different patent expiration dates. For example, our patents related to NASCOBAL® Nasal Spray expire in 2024, our patents related to AVEED® expire in 2027 and our patents related to ADRENALIN® expire in 2035.

XIAFLEX® is a biological product. We own or have licensed rights to patents and patent applications related to XIAFLEX®, including drug product and methods of manufacture patents and patent applications that will expire into the late 2030s and methods of use patents and patent applications for uses such as plantar fibromatosis that will expire into the late 2030s/early 2040s.

Our patents provide protection by allowing us to exclude others from making, using, selling, offering for sale or importing that which is covered by the patent claims. When patent protection is not feasible, we may rely on trade secrets, non-patented proprietary know-how or continuing technological innovation. Many of our products are sold under trademarks. We also rely on confidentiality agreements with our employees, consultants and other parties to protect, among other things, trade secrets and other proprietary information.

There can be no assurance that our patents, licenses or other intellectual property rights will afford us protection from competition. For example, in August 2021, the U.S. District Court for the District of Delaware held that Eagle's proposed vasopressin product did not infringe our asserted patent claims related to VASOSTRICT®. The expiration of a basic product patent or loss of patent protection resulting from a legal challenge typically results in significant competition from generic products or biosimilars against the originally patented product and can result in a significant reduction in revenues for that product in a very short period of time that may never be reversed. In some cases, however, it is possible to obtain commercial benefits from product manufacturing trade secrets, patents on uses for products, patents on processes and intermediates for the economical manufacture of the active ingredients or patents for special formulations of the product or delivery mechanisms. There can also be no assurance that our confidentiality agreements will not be breached, that we will have adequate remedies for any breach, that others will not independently develop equivalent proprietary information or that other third parties will not otherwise gain access to our trade secrets and other intellectual property.

Additionally, any pending or future patent applications made by us or our subsidiaries, our license partners or entities we may acquire in the future are subject to risks and uncertainties. The coverage claimed in any such patent applications could be significantly reduced before the patent is issued and there can be no assurance that any such applications will result in the issuance of patents or, if any patents are issued, whether they will provide significant proprietary protection or will be challenged, circumvented or invalidated. Because unissued U.S. patent applications are maintained in secrecy for a period of eighteen months and certain U.S. patent applications are not disclosed until the patents are issued, and since publication of discoveries in the scientific or patent literature often lags behind actual discoveries, we cannot be certain of the priority of inventions covered by pending patent applications. Moreover, we may have to participate in interference and other inter-parties proceedings declared by the U.S. Patent and Trademark Office (PTO) to determine priority of invention, or in opposition proceedings in a foreign patent office, either of which could result in substantial cost to us, even if the eventual outcome is favorable to us. There can be no assurance that any patents, if issued, will be held valid by a court of competent jurisdiction. An adverse outcome could subject us to significant liabilities to third parties, require disputed rights to be licensed from third parties or require us to cease using such technology. See Item 1A. Risk Factors - "Our ability to protect and maintain our proprietary and licensed third-party technology, which is vital to our business, is uncertain."

We may find it necessary to initiate litigation to enforce our patent rights, to protect our intellectual property or trade secrets or to determine the scope and validity of the proprietary rights of others. However, litigation is costly and time-consuming and there can be no assurance that we will prevail. Any successful challenges to our intellectual property rights may result in a significant loss of revenue. See Note 16. Commitments and Contingencies in the Consolidated Financial Statements included in Part IV, Item 15 of this report.

Governmental Regulation

FDA and U.S. Drug Enforcement Administration (DEA)

The pharmaceutical industry in the U.S. is subject to extensive and rigorous government regulation. The U.S. Federal Food, Drug, and Cosmetic Act (FFDCA), the U.S. Controlled Substances Act (CSA) and other federal and state statutes and regulations govern or influence the testing, manufacturing, packaging, labeling, storage, recordkeeping, approval, advertising, promotion, sale and distribution of pharmaceutical products. Noncompliance with applicable requirements can result in criminal prosecution, fines, civil penalties, recall or seizure of products, total or partial suspension of production and/or distribution, injunctions and refusal of the government to enter into supply contracts or to approve NDAs, ANDAs, BLAs and/or other similar applications.

FDA approval is typically required before any new pharmaceutical or biologic product can be marketed. An NDA or BLA is a filing submitted to the FDA to obtain approval of new chemical entities and other innovations for which thorough applied research is required to demonstrate safety and effectiveness in use. The process generally involves, among other things:

- completion of preclinical laboratory and animal testing and formulation studies in compliance with the FDA's Good Laboratory Practice regulations;
- submission to the FDA of an Investigational New Drug application (IND) for human clinical testing, which must become effective before human clinical trials may begin in the U.S.;
- approval by an independent institutional review board before each trial may be initiated and continuing review during the trial;
- performance of human clinical trials, including adequate and well-controlled clinical trials in accordance with good clinical practice, the protocol and the IND to establish the safety and efficacy of the proposed product for each intended use;
- submission to the FDA of an NDA or BLA for marketing approval, which must include data from preclinical testing and clinical trials;

- satisfactory completion of an FDA pre-approval inspection of the product's manufacturing processes and facility or facilities to assess compliance with the FDA's current Good Manufacturing Practice (cGMP) regulations and/or review of the Chemistry, Manufacturing and Controls section of the NDA or BLA to assess whether the facilities, methods and controls are adequate to preserve the proposed product's identity, strength, quality, purity and potency;
- payment of user fees for FDA review of an NDA or BLA unless a fee waiver applies;
- agreement with the FDA on the final labeling for the product and the design and implementation of any required Risk Evaluation and Mitigation Strategy (REMS);
- satisfactory completion of an FDA advisory committee review, if applicable; and
- approval by the FDA of the NDA or BLA.

Clinical trials are typically conducted in three sequential phases, although the phases may overlap or be combined. Those phases include:

- Phase 1 trials generally involve testing the product for safety, adverse effects, dosage, tolerance, absorption, distribution, metabolism, excretion and other elements of clinical pharmacology.
- Phase 2 trials typically involve a small sample of the intended patient population to assess the efficacy of the compound for a specific indication, to determine dose tolerance and the optimal dose range and to gather additional information relating to safety and potential adverse effects.
- Phase 3 trials are undertaken in an expanded patient population, typically at dispersed study sites, in order to determine the overall risk-benefit ratio of the compound and to provide an adequate basis for product labeling.

Each trial is conducted in accordance with certain standards under protocols that detail the objectives of the study, the parameters to be used to monitor safety and the efficacy criteria to be evaluated. Each protocol must be submitted to the FDA as part of the IND. Clinical trials, clinical investigators and the trial sponsor are also subject to regulatory inspections by the FDA and other regulatory authorities to confirm compliance with applicable regulatory standards. The process of completing clinical trials for a new product may take many years and require the expenditures of substantial resources. See Item 1A. Risk Factors - "The pharmaceutical industry is heavily regulated, which creates uncertainty about our ability to bring new products to market and imposes substantial compliance costs on our business, including withdrawal or suspension of existing products."

As a condition of approval of an NDA or BLA, the FDA may require further studies, including Phase 4 post-marketing studies or post-marketing data reporting, such as evaluating known or signaled safety risks. Results of post-marketing programs may limit or expand the future marketing of the products and result in the FDA requiring labeling changes, including the addition of risk information.

For some products, the FDA may require a REMS to confirm that a drug's benefits outweigh its risks. REMS could include medication guides, physician communication plans or other elements. See Item 1A. Risk Factors - "The pharmaceutical industry is heavily regulated, which creates uncertainty about our ability to bring new products to market and imposes substantial compliance costs on our business, including withdrawal or suspension of existing products."

In most instances, FDA approval of an ANDA is required before a generic equivalent of an existing or reference-listed drug can be marketed. The ANDA process is abbreviated in that the FDA waives the requirement of conducting complete preclinical and clinical studies and generally instead relies principally on bioequivalence studies. Bioequivalence generally involves a comparison of the rate of absorption and levels of concentration of a generic product in the body with those of the previously approved product. When the rate and extent of absorption of systemically acting test and reference drugs are considered the same under the bioequivalence requirement, the two products are considered bioequivalent and are generally regarded as therapeutically equivalent (so long as the products also have the same active ingredient(s), strength/concentration, dosage form and route of administration), meaning that a pharmacist can substitute the generic product for the reference-listed drug. Under certain circumstances, an ANDA may also be submitted for a product authorized by approval of an ANDA suitability petition. Such petitions may be submitted to secure authorization to file an ANDA for a product that differs from a previously approved product in active ingredient, route of administration, dosage form or strength. In September 2007 and July 2012, the U.S. Congress re-authorized pediatric testing legislation, which now requires ANDAs approved via the suitability petition route to conduct pediatric testing. The timing of final FDA approval of an ANDA application depends on a variety of factors, including whether the applicant challenges any listed patents for the reference-listed drug and whether the manufacturer of the reference-listed drug is entitled to one or more statutory exclusivity periods during which the FDA is prohibited from finally approving generic products. In certain circumstances, a regulatory exclusivity period can extend beyond the life of a patent, thus blocking ANDAs from being approved even after the patent expiration date.

Certain of our products are or could become regulated and marketed as biologic products pursuant to BLAs. Our BLA-licensed products were licensed based on a determination by the FDA of safety, purity and potency as required under the U.S. Public Health Service Act (PHSA). Although the ANDA framework referenced above does not apply to generics of BLA-licensed biologics, there is an abbreviated licensure pathway for products deemed to be biosimilar to, or interchangeable with, FDA-licensed reference biological products pursuant to the U.S. Biologics Price Competition and Innovation Act of 2009 (BPCIA). The BPCIA framework was enacted as part of the U.S. Patient Protection and Affordable Care Act (PPACA). Under the BPCIA, following the expiration of a 12-year reference exclusivity period, the FDA may license, under section 351(k) of the PHSA, a biological product that it determines is biosimilar to, or interchangeable with, a reference product licensed under section 351(a) of the PHSA. Although licensure of biosimilar or interchangeable products is generally expected to require less than the full complement of product-specific preclinical and clinical data required for innovator products, the FDA has considerable discretion over the kind and amount of scientific evidence required to demonstrate biosimilarity and interchangeability.

Some pharmaceutical products are available in the U.S. that are not the subject of an FDA-approved NDA. In 2011, the FDA's Center for Drug Evaluation and Research (CDER) Office of Compliance modified its enforcement policy with regard to the marketing of such "unapproved" marketed products (the Unapproved Drug Initiative). Under CDER's revised guidance, the FDA encourages manufacturers to obtain NDA approvals for such products by requiring unapproved versions to be removed from the market after an approved version has been introduced, subject to a grace period at the FDA's discretion. This grace period is intended to allow an orderly transition of supply to the market and to mitigate any potential related product shortage. Depending on the length of the grace period and the time it takes for subsequent applications to be approved, this may result in a period of de facto market exclusivity to the first manufacturer that has obtained an approved NDA for the previously unapproved marketed product. In November 2020, the U.S. Department of Health and Human Services (HHS) announced that it was withdrawing its Unapproved Drugs Compliance Policy Guidance and terminating the Unapproved Drug Initiative described above. However, in May 2021, HHS withdrew the November 2020 termination notice and stated that the FDA would issue new guidance on its enforcement priorities for unapproved marketed products.

OTC products may, depending on ingredients and proposed label claims, be marketed pursuant to the OTC monograph process or could require NDA or ANDA approval. The OTC monograph process allows for OTC products to be marketed without pre-market approval and generally does not require clinical studies. The U.S. Over-the-Counter Monograph Safety, Innovation, and Reform Act, enacted on March 27, 2020, modified this process by introducing administrative orders as a replacement to rulemaking for the development of OTC monographs.

Laws and regulations impacting the pharmaceutical industry are constantly evolving. For example, the U.S. 21st Century Cures Act (Cures Act), which was signed into law on December 13, 2016, includes various provisions to accelerate the development and delivery of new treatments, such as those intended to expand the types of evidence manufacturers may submit to support FDA approval, to encourage patient-centered product development, to liberalize the communication of healthcare economic information to payers and to create greater transparency with regard to manufacturer expanded access programs. Central to the Cures Act are provisions that enhance and accelerate the FDA's processes for reviewing and approving new products and supplements to approved NDAs. The Cures Act also included $1 billion in new funding to states to supplement opioid abuse prevention and treatment activities.

More recently, in December 2019, the Further Consolidated Appropriations Act, 2020 became law. Section 610 of Division N Title I, titled "*Actions for Delays of Generic Drugs and Biological Products*," provides generic (ANDA and 505(b)(2)) and biosimilar developers with a private right of action to obtain sufficient quantities of reference product from the brand manufacturer, or a generic or biosimilar manufacturer, necessary for approval of the developers' generic or biosimilar product. If a generic or biosimilar developer is successful in its suit, the defendant manufacturer would be required to provide sufficient quantities of product on commercially-reasonable, market-based terms and may be required to pay the developer's reasonable attorney's fees and costs as well as financial compensation under certain circumstances. The purpose of section 610 is to promote competition by facilitating the timely entry of lower-cost generic and biosimilar products. In addition, on March 27, 2020, Congress enacted the Coronavirus Aid, Relief, and Economic Security Act (CARES Act) in response to the COVID-19 pandemic. Among other provisions, the CARES Act made a number of changes to the FFDCA aimed at preventing drug shortages. Similarly, the FDA has issued a number of guidance documents describing the agency's expectations for how drug manufacturers should comply with various FDA requirements during the pandemic, including with respect to conducting clinical trials, distributing drug samples and reporting post-marketing adverse events. Moreover, as a result of the COVID-19 pandemic, there has been increasing political and regulatory scrutiny of foreign-sourced drugs and foreign drug supply chains, resulting in proposed legislative and executive actions, including executive orders, to incentivize or compel drug manufacturing operations to relocate to the U.S.

A sponsor of an NDA is required to identify, in its application, any patent that claims the drug or a use of the drug subject to the application. Upon NDA approval, the FDA lists these patents in a publication referred to as the Orange Book. Any person that files an ANDA or NDA under Section 505(b)(2) of the FFDCA referencing the approved drug must make a certification in respect to any listed patents for the reference drug. The FDA may not approve such an ANDA or 505(b)(2) application until expiration of the reference drug's listed patents unless: (i) the applicant certifies that the listed patents are invalid, unenforceable and/or not infringed by the proposed generic drug and gives notice to the holder of the NDA for the listed drug of the basis upon which the patents are challenged and (ii) the holder of the listed drug does not sue the later applicant for patent infringement within 45 days of receipt of notice. Under the current law, if an infringement suit is filed, the FDA may not approve the later application until the earliest of: (i) 30 months after submission; (ii) entry of an appellate court judgment holding the patent invalid, unenforceable or not infringed; (iii) such time as a court may order; or (iv) expiration of the patent.

One of the key motivators for challenging patents is the 180-day marketing exclusivity period granted to the developer of a generic version of a product that is the first to have a substantially complete ANDA received for review by the FDA and whose filing includes a certification that a reference product's listed patent(s) are invalid, unenforceable and/or not infringed (a Paragraph IV certification) and that otherwise does not forfeit eligibility for the exclusivity. Under the U.S. Medicare Prescription Drug, Improvement, and Modernization Act of 2003, with accompanying amendments to the U.S. Drug Price Competition and Patent Term Restoration Act (the Hatch-Waxman Act), this marketing exclusivity would begin to run upon the earlier of the commercial launch of the generic product or upon an appellate court decision in the generic company's favor or in favor of another ANDA applicant who had filed with a Paragraph IV certification and has tentative approval. In addition, the holder of the NDA for the listed drug may be entitled to certain non-patent exclusivity during which, depending on the type of exclusivity, the FDA either cannot accept or approve an application for a competing ANDA generic product or 505(b)(2) NDA product with the same active moiety. Depending on the exclusivity, the protection may apply to all of the reference drug's approved conditions of use, or may be limited to a certain condition of use or other protected label information.

The FDA also regulates pharmacies and outsourcing facilities that prepare "compounded" drugs pursuant to section 503A and 503B of the FFDCA, respectively. For instance, under section 503A of the FFDCA, pharmacies may compound drugs for an identified individual based on the receipt of a valid prescription order, or notation approved by the prescribing practitioner, that a compounded product is necessary for the identified patient. Similarly, under section 503B of the FFDCA, outsourcing facilities may compound drugs and sell them to healthcare providers, but not wholesalers or distributors. Although section 503A pharmacies and section 503B outsourcing facilities are subject to many regulatory requirements, compounded drugs are not subject to premarket review by the FDA and, therefore, may not have the same level of safety and efficacy as products subject to premarket review and approval by the FDA. Because they are not subject to premarket review, compounded drugs are frequently lower cost than either branded or generic products.

The FDA enforces regulations to require that the methods used in, and the facilities and controls used for, the manufacture, processing, packing and holding of drugs conform to cGMPs. The cGMP regulations the FDA enforces are comprehensive and cover all aspects of manufacturing operations. Compliance with the regulations requires a continuous commitment of time, money and effort in all operational areas.

The FDA conducts pre-approval inspections of facilities engaged in the development, manufacture, processing, packing, testing and holding of the products subject to NDAs and ANDAs and pre-license inspections of facilities engaged in similar activities for biologic products subject to BLAs. In addition, manufacturers of both pharmaceutical products and active pharmaceutical ingredients (APIs) used to formulate such products also ordinarily undergo pre-approval inspections. Failure of any facility to pass a pre-approval inspection will result in delayed approval.

Facilities that manufacture pharmaceutical or biological products must be registered with the FDA and all such products made in such facilities must be manufactured in accordance with the latest cGMP regulations. The FDA conducts periodic inspections of facilities to assess the cGMP status of marketed products. Following such inspections, the FDA could issue a Form 483 Notice of Inspectional Observations, which could require modification to certain activities identified during the inspection. If the FDA were to find serious cGMP non-compliance during such an inspection, it could take regulatory actions. The FDA also may issue an untitled letter as an initial correspondence that cites violations that do not meet the threshold of regulatory significance for a Warning Letter. FDA guidelines also provide for the issuance of Warning Letters for violations of "regulatory significance" for which the failure to adequately and promptly achieve correction may be expected to result in an enforcement action.

Imported API and other components needed to manufacture our products could be rejected by U.S. Customs. In respect to domestic establishments, the FDA could initiate product seizures or request, or in some instances require, product recalls and seek to enjoin or otherwise limit a product's manufacture and distribution. In certain circumstances, violations could support civil penalties and criminal prosecutions. In addition, if the FDA concludes that a company is not in compliance with cGMP requirements, sanctions may be imposed that include preventing that company from receiving the necessary licenses to export its products and classifying that company as an unacceptable supplier, thereby disqualifying that company from selling products to federal agencies.

Certain of our subsidiaries sell products that are “controlled substances” as defined in the CSA and implementing regulations, which establish certain security and recordkeeping requirements administered by the DEA. The DEA regulates chemical compounds as Schedule I, II, III, IV or V substances, with Schedule I substances considered to present the highest risk of substance abuse and Schedule V substances the lowest risk. The active ingredients in some of our products are listed by the DEA as Schedule II or III substances under the CSA. Consequently, their manufacture, shipment, storage, sale and use are subject to a high degree of regulation.

The DEA limits the availability of the active ingredients that are subject to the CSA used in several of our products as well as the production of these products. We or our contract manufacturing organizations must annually apply to the DEA for procurement and production quotas in order to obtain and produce these substances. As a result, our quotas may not be sufficient to meet commercial demand or complete clinical trials. Moreover, the DEA may adjust these quotas from time to time during the year, although the DEA has substantial discretion in whether or not to make such adjustments. See Item 1A. Risk Factors - “The DEA limits the availability of the active ingredients used in many of our products as well as the production of these products, and, as a result, our procurement and production quotas may not be sufficient to meet commercial demand or complete clinical trials.”

To meet its responsibilities, the DEA conducts periodic inspections of registered establishments that handle controlled substances. Annual registration is required for any facility that manufactures, tests, distributes, dispenses, imports or exports any controlled substance. The facilities must have the security, control, accounting mechanisms and monitoring systems required by the DEA to prevent loss and diversion of controlled substances and to comply with reporting obligations. Failure to maintain compliance can result in enforcement action. The DEA may seek civil penalties, refuse to renew necessary registrations or initiate proceedings to revoke or restrict those registrations or, with the U.S. Department of Justice (DOJ), seek to impose civil penalties. In certain circumstances, violations could result in criminal proceedings.

In October 2018, the U.S. Congress enacted the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (H.R. 6). Intended to achieve sweeping reform to combat opioid abuse, H.R. 6, among other provisions, amends related laws administered by the FDA, DEA and the U.S. Centers for Medicare and Medicaid Services (CMS). Among other things, the law: (i) amends requirements related to the FDA’s authority to include packaging requirements in REMS requirements; (ii) increases civil and criminal penalties for manufacturers and distributors for failing to maintain effective controls against diversion of opioids or for failing to report suspicious opioid orders; (iii) requires the DEA to estimate the amount of opioid diversion when establishing manufacturing and procurement quotas; (iv) implements expanded anti-kickback and financial disclosure provisions; and (v) authorizes HHS to implement a demonstration program which would award grants to hospitals and emergency departments to develop, implement, enhance or study alternative pain management protocols and treatments that limit the use and prescription of opioids in emergency departments.

Individual states also regulate controlled substances and we, as well as our third-party API suppliers and manufacturers, are subject to such regulation by several states with respect to the manufacture and distribution of these products.

Government Benefit Programs

As described further in Item 1A. Risk Factors, statutory and regulatory requirements for government healthcare programs such as Medicaid, Medicare and TRICARE govern access and provider reimbursement levels, and provide for other cost-containment measures such as requiring pharmaceutical companies to pay rebates or refunds for certain sales of products reimbursed by such programs, or subjecting products to certain price ceilings. In addition to the cost-containment measures described in Item 1A. Risk Factors, sales to retail pharmacies under the TRICARE Retail Pharmacy Program are subject to certain price ceilings which require manufacturers to, among other things, pay refunds for prescriptions filled based on the applicable ceiling price limits. Beginning in the first quarter of 2017, pursuant to the Bipartisan Budget Act of 2015, manufacturers are required to pay additional rebates to state Medicaid programs if the prices of their non-innovator products rise at a rate faster than inflation (as continues to be the case for innovator products); this requirement previously existed only as to branded or innovator products and the change in law may impact our business.

The federal government may continue to pursue legislation aimed at containing or reducing payment levels for prescription pharmaceuticals paid for in whole or in part with government funds. State governments also may continue to enact similar cost containment or transparency legislation. These efforts could have material consequences for the pharmaceutical industry and the Company. From time to time, legislative changes are made to government healthcare programs that impact our business. The U.S. Congress continues to examine various Medicare and Medicaid policy proposals that may result in a downward pressure on the prices of prescription products in these programs, including, for example, as part of the Inflation Reduction Act of 2022 that was enacted in August 2022. See Item 1A. Risk Factors - “The availability of third-party reimbursement for our products is uncertain, and we may find it difficult to maintain current price levels. Additionally, the market may not accept those products for which third-party reimbursement is not adequately provided.”

Under the PPACA, pharmaceutical manufacturers of branded prescription products must pay an annual fee to the federal government. Each individual pharmaceutical manufacturer must pay a prorated share of the total industry fee based on the dollar value of its branded prescription product sales to specified federal programs.

The PPACA has been subject to court challenges and repeal efforts. For example, the U.S. Tax Cuts and Jobs Act of 2017 (TCJA) repealed the requirement that individuals maintain health insurance coverage or face a penalty (known as the individual mandate). In June 2021, the U.S. Supreme Court held that state and individual plaintiffs did not have standing to challenge the minimum essential coverage provision of the PPACA; in so holding, the U.S. Supreme Court did not consider larger constitutional questions about the validity of this provision or the validity of the PPACA in its entirety. Ongoing efforts to repeal, substantially amend, eliminate or reduce funding for the PPACA may threaten the stability of the insurance marketplace and may have consequences for the coverage and accessibility of prescription drugs. The current administration has taken actions intended to strengthen and build upon the PPACA.

Healthcare Fraud and Abuse Laws

We are subject to various federal, state and local laws targeting fraud and abuse in the healthcare industry, violations of which can lead to civil and criminal penalties, including fines, imprisonment and exclusion from participation in federal healthcare programs. These laws are potentially applicable to us as both a manufacturer and a supplier of products reimbursed by federal healthcare programs, and they also apply to hospitals, physicians and other potential purchasers of our products.

The U.S. federal Anti-Kickback Statute (42 U.S.C. § 1320a-7b) prohibits persons from knowingly and willfully soliciting, receiving, offering or providing remuneration, directly or indirectly, to induce either the referral of an individual, or the furnishing, recommending or arranging for a good or service, for which payment may be made under a federal healthcare program such as the Medicare and Medicaid programs. Remuneration is not defined in the federal Anti-Kickback Statute and has been broadly interpreted to include anything of value, including for example, gifts, discounts, coupons, the furnishing of supplies or equipment, credit arrangements, payments of cash, waivers of payments, ownership interests and providing anything at less than its fair market value. Under the federal Anti-Kickback Statute and the applicable criminal healthcare fraud statutes contained within 42 U.S.C. § 1320a-7b, a person or entity need not have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the government may assert that a claim, including items or services resulting from a violation of 42 U.S.C. § 1320a-7b, constitutes a false or fraudulent claim for purposes of the civil U.S. False Claims Act (FCA), which is discussed below, or the civil monetary penalties statute, which imposes fines against any person who is determined to have presented or caused to be presented claims to a federal healthcare program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent. The federal Anti-Kickback Statute and implementing regulations provide for certain exceptions for “safe harbors” for certain discounting, rebating or personal services arrangements, among other things, which were amended in 2020. However, the lack of uniform court interpretation of the Anti-Kickback Statute, coupled with novel enforcement theories by government authorities and stayed implementation of certain regulatory changes, make compliance with the law difficult. Violations of the federal Anti-Kickback Statute can result in significant criminal fines, exclusion from participation in Medicare and Medicaid and follow-on civil litigation, among other things, for both entities and individuals.

The civil FCA and similar state laws impose liability on any person or entity who, among other things, knowingly presents, or causes to be presented, a false or fraudulent claim for payment by a federal healthcare program. The *qui tam* provisions of the FCA and similar state laws allow a private individual to bring civil actions on behalf of the federal or state government and to share in any monetary recovery. The U.S. Federal Physician Payments Sunshine Act and similar state laws impose reporting requirements for various types of payments to physicians and teaching hospitals. Failure to comply with reporting requirements under these laws could subject manufacturers and others to substantial civil money penalties. In addition, government entities and private litigants have asserted claims under state consumer protection statutes against pharmaceutical and medical device companies for alleged false or misleading statements in connection with the marketing, promotion and/or sale of pharmaceutical and medical device products, including state investigations of the Company regarding vaginal mesh devices previously sold by certain of our operating subsidiaries and investigations and litigation by certain government entities regarding the prior promotional practices of certain of our operating subsidiaries with respect to opioid products.

International Regulations

Through our international operations, the Company is subject to laws and regulations that differ from those under which the Company operates in the U.S. In most cases, non-U.S. regulatory agencies evaluate and monitor the safety, efficacy and quality of pharmaceutical products, govern the approval of clinical trials and product registrations and regulate pricing and reimbursement. Certain international markets have differing product preferences and requirements and operate in an environment of government-mandated, cost-containment programs, including price controls, such as the Patented Medicine Prices Review Board (PMPRB) in Canada.

In Canada, the *Regulations Amending the Patented Medicines Regulations (Additional Factors and Information Reporting Requirements)* (the Amendments) came into force on July 1, 2022. The Amendments made a number of changes to the regulation of Canadian drug prices by the PMPRB. The PMPRB is an administrative board with a mandate to protect Canadians from excessive pricing of patented medicines. Pharmaceutical manufacturers that are patentees are required to report applicable patents and file sales information so the PMPRB can monitor for excessive pricing as long as the product is considered to be a patented medicine. If it is determined the average price for a patented medicine is too high based on pricing tests developed by the PMPRB, a payment must be made to the PMPRB to offset the excessive revenues that were generated and/or the price of the medicine must be reduced. The PMPRB's authority to regulate the price of a drug product is linked to patent protection, specifically when there is a patent to an invention that is intended or capable of being used for medicine or for the preparation or production of medicine.

Certain governments have placed restrictions on physician prescription levels and patient reimbursements, emphasized greater use of generic products and enacted across-the-board price cuts as methods of cost control.

Whether or not FDA approval has been obtained for a product, approval of the product by comparable regulatory authorities of other governments must be obtained prior to marketing the product in those jurisdictions. The approval process may be more or less rigorous than the U.S. process and the time required for approval may be longer or shorter than in the U.S.

Environmental Matters

Our operations are subject to substantial federal, state and local environmental laws and regulations concerning, among other matters, the generation, handling, storage, transportation, treatment and disposal of, and exposure to, hazardous substances. Violation of these laws and regulations, which may change, can lead to substantial fines and penalties. Many of our operations require environmental permits and controls to prevent and limit pollution of the environment. We believe that our facilities and the facilities of our third-party service providers are in substantial compliance with applicable environmental laws and regulations. As part of our ESG strategy, we are committed to operating our business in a responsible manner that seeks to minimize environmental impact, while promoting the safe, efficient and responsible use of global resources.

Service Agreements

We contract with various third parties to provide certain critical services including manufacturing, packaging, supply, warehousing, distribution, customer service, certain financial functions, certain R&D activities and medical affairs, among others.

Refer to Note 12. License, Collaboration and Asset Acquisition Agreements and Note 16. Commitments and Contingencies in the Consolidated Financial Statements included in Part IV, Item 15 of this report for additional information.

We primarily purchase our raw materials for the production and development of our products in the open market from third-party suppliers. We attempt, when possible, to mitigate our raw material supply risks through inventory management and alternative sourcing strategies. However, some raw materials are only available from one source. We are required to identify the suppliers of all raw materials for our products in the drug applications that we file with the FDA. If the raw materials from an approved supplier for a particular product become unavailable, we would be required to qualify a substitute supplier with the FDA, which would likely interrupt manufacturing of the affected product. See Item 1A. Risk Factors for further discussion on the risks associated with the sourcing of our raw materials.

License & Collaboration Agreements and Acquisitions

We continue to seek to enhance our product line and develop a diversified portfolio of products through product acquisitions and in-licensing or acquiring licenses to products, compounds and technologies from third parties. The Company enters into strategic alliances and collaborative arrangements with third parties, which give the Company rights to develop, manufacture, market and/or sell pharmaceutical products, the rights to which are primarily owned by these third parties. These alliances and arrangements can take many forms, including licensing arrangements, co-development and co-marketing agreements, co-promotion arrangements, research collaborations and joint ventures. Such alliances and arrangements enable us to share the risk of incurring all R&D expenses that do not lead to revenue-generating products; however, because profits from alliance products are shared with the counter-parties to the collaborative arrangement, the gross margins on alliance products are generally lower, sometimes substantially so, than the gross margins that could be achieved had the Company not opted for a development partner. Refer to Note 12. License, Collaboration and Asset Acquisition Agreements in the Consolidated Financial Statements included in Part IV, Item 15 of this report for additional information.

Human Capital Resources

As of February 27, 2023, we have 2,861 employees, of which 423 are engaged in R&D and regulatory work, 356 in sales and marketing, 1,106 in manufacturing, 580 in quality assurance and 396 in general and administrative capacities. With the exception of certain production personnel in our Rochester, Michigan manufacturing facility, our employees are generally not represented by unions. We believe that our relations with our employees are good.

Information about our Executive Officers

The following table sets forth, as of March 6, 2023, information about our executive officers:

Name	Age	Position and Offices
Blaise Coleman	49	President and Chief Executive Officer
Patrick Barry	55	Executive Vice President and President, Global Commercial Operations
Mark T. Bradley	54	Executive Vice President and Chief Financial Officer
Matthew J. Maletta	51	Executive Vice President and Chief Legal Officer and Company Secretary
James P. Tursi, M.D.	58	Executive Vice President, Global Research & Development

Blaise Coleman was appointed President, Chief Executive Officer and a member of the Board of Directors, effective March 2020. He previously served as Executive Vice President and Chief Financial Officer since December 2016. He joined Endo in January 2015 as Vice President of Corporate Financial Planning & Analysis, and was then promoted to Senior Vice President, Global Finance Operations in November 2015. Prior to joining Endo, Mr. Coleman held a number of finance leadership roles with AstraZeneca, most recently as the Chief Financial Officer of the AstraZeneca/Bristol-Myers Squibb US Diabetes Alliance. Prior to that, he was the Head of Finance for the AstraZeneca Global Medicines Development organization based in Mölndal, Sweden. Mr. Coleman joined AstraZeneca in 2007 as Senior Director Commercial Finance for the US Cardiovascular Business. He joined AstraZeneca from Centocor, a wholly-owned subsidiary of Johnson & Johnson, where he held positions in both the Licenses & Acquisitions and Commercial Finance organizations. Mr. Coleman's move to Centocor in early 2003 followed 7 years' experience with the global public accounting firm, PricewaterhouseCoopers LLP. Mr. Coleman is a Certified Public Accountant; he holds a Bachelor of Science degree in accounting from Widener University and an M.B.A. from the Fuqua School of Business at Duke University.

Patrick Barry was appointed Executive Vice President and President, Global Commercial Operations, effective April 2020. In this role, he has responsibility for the Company's global commercial organization across each of Endo's four reportable business segments, including Branded Pharmaceuticals, Sterile Injectables, Generic Pharmaceuticals and International Pharmaceuticals. He formerly served as Executive Vice President and Chief Commercial Officer, U.S. Branded Business since February 2018, after joining Endo in December 2016 as Senior Vice President, U.S. Branded Pharmaceuticals. Prior to joining Endo, Mr. Barry worked at Sanofi S.A. from 1992 until December 2016, holding roles of increasing responsibility in areas such as Sales Leadership, Commercial Operations, Marketing, Launch Planning and Training and Leadership Development. Most recently, he served at Sanofi S.A. as its General Manager and Head of North America General Medicines starting in September 2015 and as Vice President and Head of U.S. Specialty from April 2014 until August 2015. During this time, Mr. Barry oversaw three complex and diverse businesses with responsibility for leading sales and marketing activities for branded and generic products across the U.S. and Canada. He has a diverse therapeutic experience including aesthetics and dermatology, oncology, urology, orthopedics and medical device and surgical experience. He has an M.B.A. from Cornell University, Johnson School of Management and a B.A. in Public Relations and Marketing from McKendree University.

Mark T. Bradley was appointed Executive Vice President and Chief Financial Officer, effective March 2020. He previously served as Senior Vice President, Corporate Development & Treasurer since June 2017. Mr. Bradley joined Endo in January 2007 as a Finance Director and has held various positions of increasing responsibility since joining the Company. Prior to joining Endo, he spent nearly 7 years as a management consultant, most recently with Deloitte Consulting, providing a broad range of strategic and operational advice and services to senior executives across a number of industries. In addition, Mr. Bradley served as a Finance Director for an industrial products company for approximately 2 years. He spent the first 5 years of his career in public accounting at Ernst & Young LLP. Mr. Bradley is a licensed Certified Public Accountant and holds a Bachelor of Science degree in Accounting from Saint Joseph's University and a Master of Business Administration from The University of Texas at Austin.

Matthew J. Maletta was appointed Executive Vice President and Chief Legal Officer, effective May 2015, where he has global responsibility for all legal matters affecting the Company. He was also appointed Company Secretary, effective June 2020. Prior to joining Endo in 2015, Mr. Maletta served as Vice President, Associate General Counsel and Corporate Secretary of Allergan. In this position, he served as an advisor to the Chief Executive Officer and Board of Directors and supervised several large transactions, including the $70 billion acquisition of Allergan by Actavis in 2015. Mr. Maletta also played a key role defending Allergan from an unsolicited takeover bid by Valeant Pharmaceuticals and Pershing Square Capital Management in 2014. Mr. Maletta joined Allergan in 2002 and during his tenure, held roles of increased responsibility, including serving as the lead commercial attorney for Allergan's aesthetics businesses for several years and as Head of Human Resources in 2010. Prior to joining Allergan, Mr. Maletta was in private practice, focusing on general corporate matters, finance, governance, securities and transactions. He holds a B.A. degree in political science from the University of Minnesota, summa cum laude and Phi Beta Kappa, and a J.D. degree, cum laude, from the University of Minnesota Law School.

James P. Tursi, M.D. was appointed Executive Vice President, Global Research & Development, effective January 2022. In this role, Dr. Tursi is responsible for leading global research & development, medical affairs and regulatory operations. Prior to joining Endo, he held senior leadership roles at Ferring Pharmaceutical U S , Antare Pharmaceutical and Aralez Pharmaceutical Prior to Aralez, Dr Tur i wa Chief Medical Officer and Vice President of Clinical R&D at Auxilium Pharmaceuticals until its acquisition by Endo in 2015. Dr. Tursi practiced medicine and surgery for over 10 years and created a medical education company, I Will Pass®, which assisted physicians in the process of board certification. He performed his residency in Gynecology and Obstetrics at the Johns Hopkins Hospital, holds a Bachelor of Science degree in Chemistry and Biology from Ursinus College and a Doctor of Medicine degree from the Medical College of Pennsylvania. Dr. Tursi is a member of the Ideal Image Board of Directors. Previously, Dr. Tursi erved a a member of the Agile Therapeutic , Inc Board of Director from October 2014 to October 2022

We have employment agreements with each of our executive officers.

Available Information

Our internet address is www.endo.com. The contents of our website are not part of this Annual Report on Form 10-K and our internet address is included in this document as an inactive textual reference only. We currently make our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, proxy reports and all amendments to those reports available free of charge on our website as soon as reasonably practicable after we file uch report with, or furni h uch report to, the SEC

You can access our filings through the SEC's internet site: www.sec.gov *(intended to be an inactive textual reference only).*

You may also access copies of the Company's filings with the Canadian Securities Administrators on SEDAR through their internet site: www.sedar.com *(intended to be an inactive textual reference only).*

Item 1A. *Risk Factors*

Risk Factor Summary

The following is a summary of the risk factors contained in this Annual Report on Form 10-K that could adversely affect our business, financial condition, results of operations and cash flows. In addition to this summary, we encourage you to carefully review the full risk factors in their entirety.

Business Related Risks

- We operate in a highly competitive industry.
- Other pharmaceutical companies may obtain approval for competing versions of our products.
- Pharmacies or outsourcing facilities may produce compounded versions of our products.
- We may fail to successfully identify, develop, maintain or introduce products.
- Uncertainties exist regarding our acquisition and licensing strategy.
- Asset sales could adversely affect our prospects and opportunities for growth.
- Third-party reimbursement for our products is uncertain.
- Price levels may be reduced because of social or political pressures.
- Our business is highly dependent upon market perceptions of us, our brands and the safety and quality of our products.
- Our business and financial condition may be adversely affected by existing or future legislation and regulations.
- Our customer concentration may adversely affect us.
- We are currently dependent on outside manufacturers for the manufacture of a significant amount of our products.
- We are dependent on third parties to supply raw materials used in our products and to provide services.
- We have limited experience in manufacturing biologic products and may encounter difficulties in our manufacturing processes.
- The DEA could limit the availability of active ingredients and the production of products.
- We rely on our ability to retain our key personnel and to continue to attract additional professional staff.
- Our operations could be disrupted if our information systems fail, if we are unsuccessful in implementing necessary upgrades or if we are subject to cyber-attacks.
- We are subject to risks related to our global operations.
- We are subject to risks regarding widespread health problems, including the recent global coronavirus.
- Supply chain and other manufacturing disruptions could negatively impact our businesses.
- We may be impacted by the effects of climate change and encounter challenges implementing sustainability-related measures.

Risks Related to Bankruptcy and Our Ordinary Shares

- We are subject to risks and uncertainties associated with the Chapter 11 Cases (as defined below).
- Delays in the Chapter 11 Cases may occur.
- The RSA (as defined below) is subject to significant conditions and milestones that may be difficult for us to satisfy.
- If the RSA is terminated, our ability to confirm and consummate the Sale (as defined below) could be materially and adversely affected.
- Even if the Sale or an alternative re tructuring tran action i con ummated, we may not be able to achieve our tated oal or continue a a oing concern.

- Our ability to prosecute the Chapter 11 Cases and consummate the Sale may be contested by third parties with litigation.
- In certain instances, a chapter 11 case may be converted to a case under chapter 7 of the Bankruptcy Code.
- Alternative plans of reorganization may be introduced, which could have less favorable terms than currently anticipated or result in significant litigation and expenses.
- As a result of the Chapter 11 Cases, our historical financial information may not be indicative of our future performance, which may be volatile.
- We may be subject to claims that will not be discharged in the Chapter 11 Cases.
- If we consummate the Sale with the Stalking Horse Bidder (as defined below), we may not have sufficient liquidity to implement an orderly wind-down process.
- The pursuit of the Chapter 11 Cases has consumed, and will continue to consume, a substantial portion of the time and attention of our management and could cause us to experience increased levels of employee attrition.
- Our current sources of financing may be insufficient to fund our cash requirements through emergence from bankruptcy.
- We may be unable to comply with restrictions imposed by the Cash Collateral Order (as defined below).
- Aspects of the Chapter 11 Cases limit the flexibility of our management team in running our business.
- The trading prices of our securities have been volatile, and investments in our securities could decline in value.
- We have no plans to pay regular dividends on our ordinary shares or to conduct ordinary share repurchases.
- Shareholder activism could cause us to incur significant expenses, hinder execution of our business strategy and impact our share price.
- Our ordinary shares are quoted on the over-the-counter market, and thus may have a limited market and lack of liquidity.
- We believe it is likely that our ordinary shares will continue to decrease in value as a result of the Chapter 11 Cases.

Litigation and Liability Related Risks

- We are regularly the subject of material legal proceedings, including significant lawsuits, product liability claims, governmental investigations and product recalls.
- We may not have and may be unable to obtain or maintain insurance adequate to cover potential liabilities.
- Public concern around the abuse of opioids or other products, including law enforcement concerns over diversion or marketing practices, regulatory efforts to combat abuse and litigation could result in costs to our business and damage our reputation.

Financial and Liquidity Related Risks

- Our ability to fund our operations, maintain adequate liquidity and meet our financing obligations is reliant on our operations, which are subject to significant risks and uncertainties.
- Potential impairments of goodwill and other intangibles may significantly impact our profitability.
- Our substantial indebtedness could adversely affect our financial position.
- We may not realize the anticipated benefits from our strategic actions.

Legal and Regulatory Related Risks

- Agreements between branded pharmaceutical companies and generic pharmaceutical companies are facing increased government scrutiny and we may be subject to additional investigations or litigation.
- We are subject to various laws and regulations pertaining to the marketing of our products and services.
- The pharmaceutical industry is heavily regulated, which creates uncertainty about our ability to bring new products to market and imposes substantial compliance costs on our business, including withdrawal or suspension of existing products.
- We are subject to complex reporting and payment obligations under Medicaid and other governmental drug pricing programs.
- Decreases in the degree to which individuals are covered by healthcare insurance could result in decreased use of our products.
- Regulatory or other factors may cause us to be unable to manufacture our products or face interruptions in the manufacturing process.
- We may fail to obtain regulatory approval or maintain compliance with requirements in non-U.S. jurisdictions.
- The use of generic products may be limited through legislative, regulatory and other efforts.
- New tariffs and evolving trade policy between the U.S. and other countries, including China, could adversely affect us.
- We are subject to information privacy and data protection laws that include penalties for noncompliance.

Intellectual Property Related Risks

- Our ability to protect and maintain our proprietary and licensed third-party technology, which is vital to our business, is uncertain.
- Third-party allegations of intellectual property infringement, unfavorable outcomes in litigation and “at-risk” product launches could adversely affect us.

Tax Related Risks

- Future changes to tax laws could materially adversely affect us.
- The IRS may not agree with the conclusion that we should be treated as a non-U.S. corporation.
- The effective rate of taxation upon our results of operations is dependent on multi-national tax considerations.

- The IRS and other taxing authorities may continue to challenge our tax positions and we may not be able to successfully maintain such positions.
- Our ability to use tax attributes to offset U.S. taxable income may be limited.

Structural and Organizational Risks

- Irish law differs from the laws in effect in the U.S. and may afford less protection to our shareholders.
- Takeover attempts will be subject to Irish Takeover Rules and subject to review by the Irish Takeover Panel.
- We are an Irish company and it may be difficult to enforce judgments against us or certain of our officers and directors.

Risk Factors

The following risk factors could adversely affect our business, financial condition, results of operations and cash flows. These are not the only risks facing the Company. Other risks and uncertainties, including those not currently known to us or that we currently deem to be immaterial, could also adversely affect our business, financial condition, results of operations and cash flows.

Business Related Risks

We operate in a highly competitive industry.

The pharmaceutical industry is intensely competitive and we face competition in both our U.S. and international branded and generic pharmaceutical businesses. Competitive factors include, without limitation, product development, technological innovation, safety, efficacy, commercialization, marketing, promotion, product quality, price, cost-effectiveness, reputation, service, patient convenience and access to scientific and technical information. Many of our competitors have, and future competitors may have, greater resources than we do, and we cannot predict with certainty the timing or impact of competitors' products and commercialization strategies. Furthermore, recent market consolidation in this industry may further concentrate financial, technical and market strength and increase competitive pressure in the industry. In addition, our competitors may make greater R&D investments and have more efficient or superior processes and systems and more experience in the development of new products that permit them to respond more quickly to new or emerging technologies and changes in customer demand which may make our products or technologies uncompetitive or obsolete. Furthermore, academic institutions, government agencies and other public and private organizations conducting research may seek patent protection and may establish collaborative arrangements for competitive products or programs. If we fail to compete successfully, it could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Certain of our branded products do not currently compete with on-market generic products but are likely to face generic competition in the future. The entrance of generic competitors can occur at any time and cannot be predicted with certainty. For additional information on our patent protection, refer to Part I, Item 1 of this report "Business" under the caption "Patents, Trademarks, Licenses and Proprietary Property." Generic products we currently sell with generic exclusivity could in the future be subject to competition from other generic competitors. Some of our other branded and generic products, such as VASOSTRICT®, already face generic competition and are at risk of additional generic competitors entering the market. During the first quarter of 2022, multiple competitive generic alternatives to VASOSTRICT® were launched, beginning with a generic that was launched at risk and began shipping toward the end of January 2022. Since then, additional competitive alternatives entered the market, including authorized generics.

Manufacturers of generic products typically invest far less in R&D than research-based companies. Additionally, generic competitors, including Asian or other overseas generic competitors, may be able to manufacture products at costs lower than us. For these reasons, competitors may price their products lower than ours, and such differences could be significant. Due to lower prices, generic versions, where available, may be substituted by pharmacies or required in preference to branded versions under third-party reimbursement programs. As a result, generic competition could have a material adverse effect on our business, financial condition, results of operations and cash flows. Legislation encouraging early and rapid approval of generic drugs could also increase the degree of generic competition we face. See the risk factor "If other pharmaceutical companies use litigation and regulatory means to obtain approval for generic, biosimilar, OTC or other competing versions of our products, our sales may suffer" for more information.

In addition, our generics business faces competition from brand-name pharmaceutical companies, which have taken and may continue to take aggressive steps to thwart or delay competition from generic equivalents of their brand-name products, including bringing litigation alleging patent infringement or other violations of intellectual property rights. The actions taken by competing brand-name pharmaceutical companies may increase the costs and risks associated with our efforts to introduce generic products and may delay or prevent such introduction altogether. For example, if a brand-name pharmaceutical company's patent were held to be valid and infringed by our generic products in a particular jurisdiction, we would be required to either obtain a license from the patent holder or delay or cease the manufacture and sale of such generic product. Any of these factors could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Our sales may also suffer as a result of changes in consumer demand for our products, including as a result of fluctuations in consumer buying patterns, changes in market conditions or actions taken by our competitors, including the introduction of new products or price reductions for existing products. Any of these factors could have a material adverse effect on our business, financial condition, results of operations and cash flows.

If other pharmaceutical companies use litigation and regulatory means to obtain approval for generic, biosimilar, OTC or other competing versions of our products, our sales may suffer.

Various manufacturers have filed ANDAs seeking FDA approval for generic versions of certain of our key pharmaceutical products including, but not limited to, VASOSTRICT®, ADRENALIN® and AVEED®. In connection with such filings, these manufacturers have challenged the validity and/or enforceability of one or more of the underlying patents protecting our products.

Any launch of competing versions of any of our products could decrease the revenue of such products, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Our practice is to vigorously defend and pursue all available legal and regulatory avenues in defense of the intellectual property rights protecting our products. Despite our efforts, litigation is inherently uncertain, and we cannot predict the timing or outcome of our efforts. If we are not successful in defending our intellectual property rights or opt to settle, or if a product's marketing or data exclusivity rights expire or become otherwise unenforceable, our competitors could ultimately launch generic, biosimilar, OTC or other competing versions of our products. Upon the loss or expiration of patent protection for one of our products, or upon the "at-risk" launch (despite pending patent infringement litigation against the generic product) by a generic manufacturer of a generic version of one of our patented products, our sales and revenues of the affected products would likely decline rapidly and materially, which could require us to write off a portion or all of the intangible assets associated with the affected product and could have a material adverse effect on our business, financial condition, results of operations and cash flows.

For example, in the case of VASOSTRICT®, beginning in April 2018, Par Sterile Products, LLC (PSP LLC) and Par Pharmaceutical, Inc. (PPI) received notice letters from Eagle and other companies advising of the filing by such companies of ANDAs/NDAs for generic versions of VASOSTRICT® (vasopressin IV solution (infusion)) 20 units/ml and/or 200 units/10 ml. Beginning in May 2018, PSP LLC, PPI and Endo Par Innovation Company, LLC (EPIC) filed lawsuits against Eagle and other generic filers in the U.S. District Court for the District of Delaware or New Jersey. We reached settlements and voluntarily dismissed the suits against many of these filers. The remaining Delaware cases against Eagle and Amneal Pharmaceuticals LLC were consolidated and a trial was held in July 2021. In August 2021, the court issued an opinion holding that Eagle's proposed generic product would not infringe PPI's asserted patent claims. The court made no finding regarding the validity of the patents. We appealed the ruling. In August 2022, the Federal Circuit affirmed the District of Delaware's decision: (i) that Eagle's proposed generic product would not infringe PPI's asserted patent claims and (ii) denying the issuance of a declaratory judgment that Eagle's planned sale of generic product would infringe under 35 U.S.C. § 271(a) and (b). During the first quarter of 2022, multiple competitive generic alternatives to VASOSTRICT® 20 units/ml were launched, beginning with Eagle's generic that was launched at risk and began shipping toward the end of January 2022. Since then, additional competitive alternatives entered the market, including authorized generics. These launches began to significantly impact both Endo's market share and product price toward the middle of the first quarter of 2022, and the effects of competition have since increased. This competition could have a material adverse effect on our business, financial condition, results of operations and cash flows.

There are currently pending legal proceedings brought by us and/or our subsidiaries and, in certain cases, our third-party partners, against manufacturers seeking FDA approval for generic versions of our products. For a description of the material related legal proceedings, see Note 16. Commitments and Contingencies in the Consolidated Financial Statements included in Part IV, Item 15 of this report.

We also believe it is likely that manufacturers may seek FDA approvals for generic, OTC or other competing versions of other of our key pharmaceutical products, either through the filing of ANDAs, through the OTC monograph process or through the use of other means.

If pharmacies or outsourcing facilities produce compounded versions of our products, our sales may suffer.

Compounded drugs do not typically require the same R&D investments as either branded or generic drugs and, therefore, can compete favorably on price with both branded and generic versions of a drug. See "Governmental Regulation" in Part I, Item 1. The introduction of compounded versions of our products by pharmacies or outsourcing facilities could have a material adverse effect on our business, financial condition, results of operations and cash flows.

If we fail to successfully identify and develop additional branded and generic pharmaceutical products, obtain and maintain exclusive marketing rights for our branded and generic products or fail to introduce branded and generic products on a timely basis, our revenues, gross margin and operating results may decline.

Our financial results depend, to a significant extent, upon our ability, and the ability of our partners, to identify, develop, obtain regulatory approval for, launch and commercialize a pipeline of commercially successful branded and generic products, including first-to-file or first-to-market opportunities. Due to the significant competition we face and the importance of being the first (or one of the first) to market, no assurances can be given that we will be able to develop, introduce and maintain commercially successful products in the future. Competition could cause our revenues to decrease significantly, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Identifying and developing additional product candidates are prone to risks of failure inherent in product development. We conduct R&D to enable us to manufacture and market pharmaceutical products in accordance with specific government regulations. Much of our product development effort is focused on technically difficult-to-formulate products and/or products that require advanced manufacturing technology. Typically, expenses related to research, development and regulatory approval of compounds for our branded products are significantly greater than those expenses associated with generic products. Should we expand our R&D efforts, our research expenses are likely to increase. Because of the inherent risk associated with R&D efforts in the healthcare industry, particularly with respect to new products, our R&D expenditures may not result in the successful regulatory approval and introduction of new products and failure in the development of any new product can occur at any point in the process, including late in the process after substantial investment. Also, after we submit a regulatory application, the relevant governmental health authority may require that we conduct additional studies, including, for example, studies to assess the product's interaction with alcohol. As a result, we may be unable to reasonably predict the total R&D costs to develop a particular product and there is a significant risk that the funds we invest in R&D will not generate financial returns. In addition, our operating results and financial condition may fluctuate as the amount we spend to research and develop, commercialize, acquire or license new products, technologies and businesses changes.

The process of developing and obtaining regulatory approvals for new products is time-consuming, costly and inherently unpredictable. Even if we are able to identify and develop additional product candidates, we may fail to obtain exclusive marketing rights, such as the 180-day ANDA first-filer marketing exclusivity period provided for in the Hatch-Waxman amendments to the FFDCA or the 180-day exclusivity for competitive generic therapies established by the FDA Reauthorization Act of 2017, for such product candidates. Even if we were to secure such exclusivities, risks associated with securing timely approval, as well as risks of unfavorable litigation dispositions, put such exclusivities at risk of being forfeited. The approval of our ANDAs may also be stayed by the FDA for up to 30 months if such ANDAs become the subject of patent litigation. Even where we are awarded marketing exclusivity, we may be required to share our exclusivity period with other ANDA applicants or with authorized generics that are not prohibited from sale during the 180-day marketing exclusivity period. Our revenues have historically included sales of generic products with limited competition resulting from marketing exclusivity or other factors, and the failure to timely and effectively file any NDA, ANDA, BLA or Supplemental Biologics License Application (sBLA) with the FDA or similar filings with other regulatory agencies, or to partner with parties that have obtained marketing exclusivity, could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Furthermore, the successful commercialization of a product is subject to a number of factors, including:

- the effectiveness, ease of use and safety of our products as compared to existing products;
- customer demand and the willingness of physicians and customers to adopt our products over products with which they may have more loyalty or familiarity and overcoming any biases toward competitors' products or against our products;
- the cost of our products compared to alternative products and the pricing and commercialization strategies of our competitors;
- the success of our launch and marketing efforts;
- adverse publicity about us, our products, our competitors and their products or the industry as a whole or favorable publicity about competitors or their products;
- the advent of new and innovative alternative products;
- any unforeseen issues or adverse developments in connection with our products and any resulting litigation, regulatory scrutiny and/or harm to our reputation; and
- other risks that may be out of our control, including the decision by a collaboration partner to make substantial changes to a product's formulation or design, or a collaboration partner refusing to perform its obligations under our collaboration agreement, which may cause delays and additional costs in developing and marketing a product.

The success of our acquisition and licensing strategy is subject to uncertainty and acquisitions or licenses may reduce our earnings, be difficult to integrate, not perform as expected or require us to obtain additional financing.

We regularly evaluate selective acquisitions and look to continue to enhance our product line by acquiring rights to additional products and compounds. Such acquisitions may be carried out through corporate acquisitions, asset acquisitions, licensing or joint venture arrangements. However, we may not be able to complete acquisitions, obtain licenses or enter into arrangements that meet our target criteria on satisfactory terms, if at all. For example, we may not be able to identify suitable acquisition candidates. In addition, any acquisition of assets and rights to products and compounds may fail to accomplish our strategic objective and may not perform as expected. Further, if we are unable to maintain, on commercially reasonable terms, product, compound or other licenses that we have acquired, our ability to develop or commercialize our products may be inhibited. In order to continue to develop and broaden our product range, we must compete to acquire assets. Our competitors may have greater resources than us and therefore be better able to complete acquisitions or licenses, which could cause us to be unable to consummate acquisitions, licensing agreements or cause the ultimate price we pay to increase. If we fail to achieve our acquisition or licensing goals, our growth may be limited.

Acquisitions of companies may expose us to additional risks, which may be beyond our control and may have a material adverse effect on our business, financial condition, results of operations and cash flows. The combination of two independent businesses is a complex, costly and time-consuming process. As a result, we may be required to devote significant management attention and resources to the integration of an acquired business into our practices and operations. Any integration process may be disruptive and may not achieve realization of expected benefits. The difficulties of combining operations of companies include, among others:

- diversion of management’s attention to integration matters;
- difficulties in achieving anticipated cost or tax savings, synergies, business opportunities and growth prospects from the combination of the businesses;
- difficulties in the integration of operations and systems;
- the impact of pre-existing legal and/or regulatory issues;
- difficulties in conforming standards, controls, procedures and accounting and other policies, business cultures and compensation structures between the companies;
- difficulties in the assimilation of employees and retention of key personnel;
- difficulties in managing the expanded operations of a larger and more complex company;
- challenges in retaining existing customers and obtaining new customers;
- potential unknown liabilities or larger liabilities than projected;
- unforeseen increases to expenses or other adverse consequences; and
- difficulties in coordinating a geographically dispersed organization.

In addition, any acquisitions may result in material unanticipated problems, expenses, liabilities, competitive responses and loss or disruption of relationships with customers, suppliers, partners, regulators and others with whom we have business or other dealings.

The benefits of mergers and acquisitions are also subject to a variety of other factors, many of which are beyond our ability to control, such as changes in the rate of economic growth in jurisdictions in which the combined company will do business, the financial performance of the combined business in various jurisdictions, currency exchange rate fluctuations and significant changes in trade, monetary or fiscal policies, including changes in interest rates and tax law of the jurisdictions in which the combined company will do business. The impact of these factors, individually and in the aggregate, is difficult to predict, in part because the occurrence of the events or circumstances relating to such factors may be interrelated, and the impact to the combined company of the occurrence of any one of these events or circumstances could be compounded or, alternatively, reduced, offset or more than offset by the occurrence of one or more of the other events or circumstances relating to such factors.

In addition, based on current acquisition prices in the pharmaceutical industry, acquisitions could decrease our net income per share and add significant intangible assets and related amortization or impairment charges. Our acquisition strategy may require us to obtain additional debt or equity financing, resulting in additional debt obligations, increased interest expense or dilution of equity ownership. We may not be able to finance acquisitions on terms satisfactory to us, or at all.

We may decide to sell assets, which could adversely affect our prospects and opportunities for growth.

In addition to our efforts to consummate the Sale, and subject to any required approvals of the Bankruptcy Court, we may from time to time consider selling certain assets if we determine that such assets are not critical to our strategy or we believe the opportunity to monetize the asset is attractive or for various other reasons, including for the reduction of indebtedness. For example, as further discussed in Note 4. Discontinued Operations and Asset Sales in the Consolidated Financial Statements included in Part IV, Item 15 of this report, in both 2021 and 2022, we divested of certain assets related to our retail generics business. We have also divested of certain intellectual property rights throughout each of the past three years. We intend to continue to explore the sale of certain non-core assets, subject to any limitations imposed as a result of our bankruptcy proceedings. Although our preference is to engage in asset sales only if they advance or otherwise support our overall strategy, we may decide to sell assets in response to liquidation or other claims described herein, and any such sale could reduce the size or scope of our business, our market share in particular markets or our opportunities with respect to certain markets, products or therapeutic categories. As a result, any such sale could have a material adverse effect on our business, financial condition, results of operations and cash flows.

The availability of third-party reimbursement for our products is uncertain, and we may find it difficult to maintain current price levels. Additionally, the market may not accept those products for which third-party reimbursement is not adequately provided.

Our ability to commercialize our products depends, in part, on the extent to which reimbursement for the costs of these products is available from government healthcare programs, such as Medicaid and Medicare, private health insurers and others. We cannot be certain that, over time, third-party reimbursements for our products will be adequate for us to maintain price levels sufficient for realization of an appropriate return on our investment. Government payers, private insurers and other third-party payers are increasingly attempting to contain healthcare costs by: (i) limiting both coverage and the level of reimbursement (including adjusting co-pays) for products; (ii) refusing, in some cases, to provide any coverage for off-label uses for products; and (iii) requiring or encouraging, through more favorable reimbursement levels or otherwise, the substitution of generic alternatives to branded products. For instance, government agencies or third-party payers could attempt to reduce reimbursement for physician administered products through their interpretation of complex government price reporting obligations and payment and reimbursement coding rules, and could attempt to reduce reimbursement for separate physician administered products that share an active ingredient by requiring the blending of sales and pricing information in the same payment and reimbursement code.

There have been several recent U.S. Congressional inquiries, hearings and proposed and enacted federal and state legislation and rules, as well as executive orders, designed to, among other things: (i) reduce or limit the prices of drugs and make them more affordable for patients, such as by tying the prices that Medicare reimburses for physician administered drugs to the prices of drugs in other countries; (ii) reform the structure and financing of Medicare Part D pharmaceutical benefits, including through increasing manufacturer contributions to offset Medicare beneficiary costs; (iii) bring more transparency to how manufacturers price their medicines; (iv) enable the government to directly negotiate prices for drugs covered under Medicare; (v) revise rules associated with the calculation of Medicaid Average Manufacturer Price and Best Price, including with regard to the manner in which pharmaceutical manufacturers may provide copayment assistance to patients and the identification of “line extension” drugs, which affect the amount of rebates that manufacturers must pay on prescription drugs under Medicaid; (vi) eliminate anti-kickback statute discount safe harbor protection for manufacturer rebate arrangements with Medicare Part D Plan Sponsors and pharmacy benefit managers on behalf of Part D Plan Sponsors; (vii) create new anti-kickback statute safe harbors applicable to certain point-of-sale discounts to patients and fixed-fee administrative fee payment arrangements with pharmacy benefit managers; and (viii) and facilitate the importation of certain lower-cost drugs from other countries. In addition, state legislatures have enacted legislation and regulations designed to control pharmaceutical and biological product pricing, including restrictions on pricing or reimbursement at the state government level, marketing cost disclosure and transparency measures, and, in some cases, policies to encourage importation of drugs from other countries (subject to federal approval) and bulk purchasing, including the National Medicaid Pooling Initiative. While we cannot predict the final form of any pending legislative, regulatory and/or administrative measures, some of the pending and enacted legislative proposals or executive rulemaking, such as those incorporating International Pricing Index or Most-Favored-Nation models, could significantly reduce the coverage and levels of reimbursement for products.

In addition, in August 2022, the U.S. enacted the Inflation Reduction Act of 2022. Subject to subsequent rulemaking, this act, among other changes: (i) gives HHS the ability and authority to directly negotiate with manufacturers the price that Medicare will pay for certain drugs; (ii) requires manufacturers of certain Part B and Part D drugs to issue rebates to HHS based on certain calculations and triggers, such as when drug price increases outpace the rate of inflation; (iii) places certain limitations on out-of-pocket spending for Medicare Part D enrollees; (iv) implements a 15% corporate alternative minimum tax on book income on corporations whose average annual adjusted financial statement income during the most recently-completed three-year period exceeds $1.0 billion; (v) implements a 1% excise tax on net stock repurchases; and (vi) implements several tax incentives to promote clean energy. While the impact of the Inflation Reduction Act of 2022 was not material to us in 2022, we are continuing to evaluate the act and its requirements, as well as any potential impact on our business. It is possible that the act will have a material adverse effect on our business, financial condition, results of operations and cash flows in the future.

The unavailability of or a reduction in the reimbursement of our products could have a material adverse effect on our business, financial condition, results of operations and cash flows.

We may experience pricing pressure on our products due to social or political pressures, which would reduce our revenue and future profitability.

We may experience downward pricing pressure on our products due to social or political pressures, which would reduce our revenue and future profitability. Price increases have resulted in increased public and governmental scrutiny of the cost of pharmaceutical products. For example, U.S. federal prosecutors have issued subpoenas to pharmaceutical companies in connection with an investigation into pricing practices conducted by the DOJ. Several state attorneys general also have commenced drug pricing investigations and filed lawsuits against pharmaceutical companies, including PPI, and the U.S. Senate has investigated a number of pharmaceutical companies relating to price increases and pricing practices. Our revenue and future profitability could be negatively affected if these or other inquiries were to result in legislative or regulatory proposals limiting our ability to increase or maintain the prices of our products.

In addition, the federal government and a number of federal legislators continue to scrutinize pharmaceutical prices and seek ways to lower prices. For example, recent legislation, including the Inflation Reduction Act of 2022, seeks to reduce prescription drug costs in a variety of ways.

Our business is highly dependent upon market perceptions of us, our brands and the safety and quality of our products and similar products, and may be adversely impacted by negative publicity or findings.

We are dependent on market perceptions and consumer preferences. Negative publicity or findings associated with product quality, safety, efficacy, patient illness, side effects or other adverse effects related to, or perceived to be related to, our products, or similar products, or our or our partners' and suppliers' manufacturing facilities, could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Market perceptions and consumer preferences are very important to our business, especially with respect to our brands, company name and the safety and quality of our products. Our products and similar products are subject to market withdrawal or recall and may be claimed or proven to be ineffective or harmful to consumers.

Our products may cause known or unknown adverse or other side effects. If we or our partners, suppliers or brands are negatively impacted by publicity, media coverage, market perception or consumer preference, it could impact the commercial viability of our products, which could have a material adverse effect on our business, financial condition, results of operations and cash flows. For example, in December 2022, we announced we would be taking certain actions to cease the production and sale of QWO® in light of market concerns about the extent and variability of bruising following initial treatment as well as the potential for prolonged skin discoloration.

The pharmaceutical supply chain has been increasingly challenged by the vulnerability of distribution channels to illegal counterfeiting and the presence of counterfeit products in a growing number of markets and over the internet. Third parties may illegally distribute and sell counterfeit versions of our products that do not meet the rigorous manufacturing and testing standards that our products undergo. Counterfeit products are frequently unsafe or ineffective and can be potentially life-threatening. Counterfeit medicines may contain harmful substances, the wrong dose of API or no API at all. However, to distributors and users, counterfeit products may be visually indistinguishable from the authentic version.

Negative posts or comments about us on any social networking website could seriously damage our reputation. The inappropriate use of certain social media vehicles could cause brand damage or information leakage or could lead to legal implications from the improper collection and/or dissemination of personally identifiable information or the improper dissemination of material non-public information.

Unfavorable media coverage about opioid abuse could negatively affect our business, financial condition and results of operations. In recent years, opioid abuse has received a high degree of media coverage. Unfavorable publicity regarding, for example, the use or misuse of oxycodone or other prescription opioid medications, the limitations of abuse-deterrent forms, public inquiries and investigations into drug abuse, including the abuse of prescription products, litigation or regulatory activity could adversely affect our reputation. Additionally, increased scrutiny of opioids generally, whether focused on our products or otherwise, could negatively impact our relationship with healthcare providers and other members of the healthcare community. Such negative publicity could have an adverse effect on the potential size of the market for new or existing products and could decrease revenues and royalties, any of which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Our business and financial condition may be adversely affected by existing or future legislation and regulations.

We cannot predict with any certainty how existing laws may be applied or how laws or legal standards may change in the future. Current or future legislation and regulations, whether state or federal, or in any of the non-U.S. jurisdictions with authority over our operations, may have a material adverse effect on our business, financial condition, results of operations and cash flows.

In October 2018, the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act was enacted in response to the opioid abuse epidemic. State laws have been enacted such as the New York Opioid Stewardship Act enacted in April 2018 which provides for certain manufacturers and distributors to make payments to an opioid stewardship fund. In April 2019, New York enacted an excise tax on the first sale of every opioid unit in New York. In October 2018, the Canadian province of British Columbia enacted a statute called the Opioid Damages and Health Care Costs Recovery Act, which allows the British Columbia government to file a direct action against opioid manufacturers and wholesalers to recover the health care costs it has incurred, and will incur, resulting from an "opioid-related wrong." These statutes, and similar statutes enacted by other jurisdictions, and resultant litigation, could have a material adverse effect on our business, financial condition, results of operations and cash flows.

In Canada, the prices of patented pharmaceutical products are subject to regulation by the PMPRB. Under the Canadian Patent Act and Patented Medicines Regulations, patentees of inventions that pertain to pharmaceutical products sold in Canada are required to file price and sales information about their patented pharmaceutical products with the PMPRB. The PMPRB reviews this information on an ongoing basis to ensure that the prices of patented pharmaceuticals sold in Canada are not excessive, based upon price tests established by the PMPRB. There is a risk that the price of our pharmaceutical products could be found to be excessive because the price as set at launch is non-compliant with the PMPRB's guidelines, or because our average sale prices over time are not compliant with the guidelines. Furthermore, amendments that came into force on July 1, 2022 made a number of changes to the regulation of Canadian drug prices by the PMPRB. The application of new price tests under the PMPRB guidelines could result in the current prices of our pharmaceutical products being deemed to be excessive. Failure by us to comply with the current or future guidelines could ultimately result in us reducing the prices of the pharmaceutical products we sell in Canada and/or making payments to the Canadian government to offset revenues deemed by the PMPRB to be excessive, which could ultimately impact the commercial viability of products we sell in Canada, reduce the revenues and cash flows of our International Pharmaceuticals segment and/or could have a material adverse effect on our business, financial condition, results of operations and cash flows.

It is possible that these or other changes in law could have a material adverse effect on our business, financial condition, results of operations and cash flows. See "Governmental Regulation" in Part I, Item 1.

Our customer concentration may adversely affect our financial condition and results of operations.

We primarily sell our products to wholesalers, retail drug store chains, supermarket chains, mass merchandisers, distributors, mail order accounts, hospitals and/or government agencies. Our wholesalers and/or distributors purchase products from us and, in turn, supply products to retail drug store chains, independent pharmacies, hospitals, long-term care facilities, clinics, home infusion pharmacies, government facilities and MCOs. Our current customer group reflects significant consolidation in recent years, marked by mergers and acquisitions and other alliances. Consolidations and joint purchasing arrangements have resulted in increased pricing and other competitive pressures on pharmaceutical companies, including us. Additionally, the emergence of large buying groups representing independent retail pharmacies and other distributors and the prevalence and influence of MCOs and similar institutions have increased the negotiating power of these groups, enabling them to attempt to extract various demands, including without limitation price discounts, rebates and other restrictive pricing terms. These competitive trends could continue in the future and could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Net revenues from direct customers that accounted for 10% or more of our total consolidated net revenues during the years ended December 31, 2022, 2021 and 2020 are as follows:

	2022	2021	2020
AmerisourceBergen Corporation	35 %	36 %	33 %
McKesson Corporation	26 %	32 %	27 %
Cardinal Health, Inc.	20 %	22 %	24 %

Revenues from these customers are included within each of our segments. Accordingly, our revenues, financial condition or results of operations may also be unduly affected by fluctuations in the buying or distribution patterns of these customers. These fluctuations may result from seasonality, pricing, wholesaler inventory objectives or other factors. In addition, if we were to lose the business of any of these customers, or if any were to fail to pay us on a timely basis, it could have a material adverse effect on our business, financial condition, results of operations and cash flows.

We are currently dependent on outside manufacturers for the manufacture of a significant amount of our products; therefore, we have and expect to continue to have limited control of the manufacturing process and related costs. Certain of our manufacturers currently constitute the sole source of one or more of our products.

Third-party manufacturers currently manufacture a significant amount of our products pursuant to contractual arrangements. Certain of our manufacturers currently constitute the sole source of our products. For example, Teikoku Seiyaku Co., Ltd. is our sole source of our lidocaine patch 5% product. As a result of the sale of certain of our manufacturing facilities and related assets, as further discussed in Note 4. Discontinued Operations and Asset Sales in the Consolidated Financial Statements included in Part IV, Item 15 of this report, our reliance on third-party manufacturers has increased and we are working with new third-party manufacturers that we have not worked with before. Because of contractual restraints and the lead-time necessary to obtain FDA approval and/or DEA registration of a new manufacturer, there are no readily accessible alternatives to these manufacturers and replacement of any of these manufacturers may be expensive and time consuming and may cause interruptions in our supply of products to customers. Our business and financial viability are dependent on these third-party manufacturers for continued manufacture of our products, the continued regulatory compliance of these manufacturers and the strength, validity and terms of our various contracts with these manufacturers. Any interruption or failure by these manufacturers to meet their obligations pursuant to various agreements with us on schedule or in accordance with our expectations, or any termination by these manufacturers of our supply arrangements, which, in each case, could be the result of one or many factors outside of our control, could delay or prevent our ability to achieve sales expectations, cause interruptions in our supply of products to customers, cause us to incur failure-to-supply penalties, disrupt our operations or cause reputational harm to our company, any or all of which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

We are dependent on third parties to supply raw materials used in our products and to provide services for certain core aspects of our business. Any interruption, mistake or failure by suppliers, distributors and collaboration partners to meet their obligations pursuant to various agreements with us could have a material adverse effect on our business, financial condition, results of operations and cash flows.

We rely on third parties to supply raw materials used in our products. In addition, we rely on third-party suppliers, distributors and collaboration partners to provide services for certain core aspects of our business, including manufacturing, packaging, shipping, warehousing, distribution, customer service support, medical affairs services, clinical studies, sales and other technical and financial services. Third-party suppliers and contractors are subject to FDA and very often DEA requirements. Our business and financial viability are dependent on the continued supply of goods and services by these third parties, the regulatory compliance of these third parties and on the strength, validity and terms of our various contracts with these third parties. Any interruption, mistake or failure by our suppliers, distributors and collaboration partners to meet their obligations pursuant to various agreements with us on schedule or in accordance with our expectations, or any termination by these third parties of their arrangements with us, which, in each case, could be the result of one or many factors outside of our control, could delay or prevent the development, approval, manufacture or commercialization of our products, result in non-compliance with applicable laws and regulations, cause us to incur failure-to-supply penalties, disrupt our operations or cause reputational harm to our company, any or all of which could have a material adverse effect on our business, financial condition, results of operations and cash flows. We may also be unsuccessful in resolving any underlying issues with such suppliers, distributors and partners or replacing them within a reasonable time and on commercially reasonable terms.

APIs imported into the European Union (EU) must be certified as complying with the good manufacturing practice standards established by the EU, as stipulated by the International Conference for Harmonization. These regulations place the certification requirement on the regulatory bodies of the exporting countries. Accordingly, the national regulatory authorities of each exporting country must: (i) ensure that all manufacturing plants within their borders that export API into the EU comply with EU manufacturing standards and (ii) for each API exported, present a written document confirming that the exporting plant conforms to EU manufacturing standards. The imposition of this responsibility on the governments of the nations exporting API may cause a shortage of API necessary to manufacture our products, as certain governments may not be willing or able to comply with the regulation in a timely fashion, or at all. A shortage in API may cause us to cease manufacturing of certain products or to incur costs and delays to qualify other suppliers to substitute for those API manufacturers unable to export. This could have a material adverse effect on our business, financial condition, results of operations and cash flows.

We are dependent on third parties to provide us with various estimates as a basis for our financial reporting. While we undertake certain procedures to review the reasonableness of this information, we cannot obtain absolute assurance over the accounting methods and controls over the information provided to us by third parties. As a result, we are at risk of them providing us with erroneous data which could impact our reporting. Refer to “CRITICAL ACCOUNTING ESTIMATES” in Part II, Item 7 of this report “Management’s Discussion and Analysis of Financial Condition and Results of Operations” for information about our most significant accounting estimates.

We have limited experience in manufacturing biologic products and may encounter difficulties in our manufacturing processes, which could materially adversely affect our results of operations or delay or disrupt the manufacture and supply of those products which are reliant upon our manufacturing operations.

The manufacture of biologic products requires significant expertise and capital investment. Although we manufacture CCH, which is included in XIAFLEX®, in our Horsham, Pennsylvania facility, we have limited experience in manufacturing biologic products. Biologics such as CCH require processing steps that are highly complex and generally more difficult than those required for most chemical pharmaceuticals. In addition, TESTOPEL® is manufactured using a unique, proprietary process. If the manufacturing processes are disrupted at the facilities where our biologic products are manufactured, it may be difficult to find alternate manufacturing sites. We may encounter difficulties with the manufacture of CCH and the active ingredient of TESTOPEL®, which could delay, disrupt or halt our manufacture of such products and/or product candidates, result in supply disruption or delay, product recalls or product liability claims, require write-offs or otherwise have a material adverse effect on our business, financial condition, results of operations and cash flows.

The DEA limits the availability of the active ingredients used in many of our products as well as the production of these products, and, as a result, our procurement and production quotas may not be sufficient to meet commercial demand or complete clinical trials.

The DEA limits the availability of the active ingredients used in many of our products and sets a quota on the production of these products. We, or our contract manufacturing organizations, must annually apply to the DEA for procurement and production quotas in order to obtain these substances and produce our products. In addition, H.R. 6 amended the CSA with respect to quotas by requiring the DEA to estimate the amount and impact of diversion (including overdose deaths and abuse and overall public health impact) of fentanyl, oxycodone, hydrocodone, oxymorphone or hydromorphone and to make appropriate quota reductions. As a result, our procurement and production quotas may not be sufficient to meet commercial demand or to complete clinical trials. Moreover, the DEA may adjust these quotas from time to time during the year. Any delay or refusal by the DEA in establishing our quotas, or modification of our quotas, for controlled substances could delay or result in the stoppage of clinical trials or product launches, or could cause trade inventory disruptions for those products that have already been launched, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

If we are unable to retain our key personnel and continue to attract additional professional staff, we may be unable to maintain or expand our business.

Because of the specialized scientific nature of our business, our ability to develop products and to compete with our current and future competitors will remain highly dependent, in large part, upon our ability to attract and retain qualified scientific, technical and commercial personnel. The loss of key scientific, technical and commercial personnel or the failure to recruit additional key scientific, technical and commercial personnel could have a material adverse effect on our business, financial condition, results of operations and cash flows. While we have consulting agreements with certain key individuals and institutions and have employment agreements with our key executives, we may be unsuccessful in retaining personnel or their services under existing agreements. There is intense competition for qualified personnel in our industry, and we may be unable to continue to attract and retain the qualified personnel necessary for the successful development of our business. These risks have been and are likely to continue to be exacerbated by our ongoing bankruptcy proceedings.

Our operations could be disrupted if our information systems fail, if we are unsuccessful in implementing necessary upgrades or if we are subject to cyber-attacks.

Our business depends on the efficient and uninterrupted operation of our computer and communications systems and networks, hardware and software systems and our other information technology. As such, we continuously invest financial and other resources to maintain, enhance, further develop, replace or add to our information technology infrastructure. Such efforts carry risks such as cost overruns, project delays and business interruptions, which could have a material adverse effect on our business, financial condition, results of operations and cash flows. Additionally, these measures are not guaranteed to protect against all cybersecurity incidents.

In the ordinary course of our business, we collect and maintain information, which includes confidential, proprietary and personal information regarding our customers and employees, in digital form. Data maintained in digital form is subject to risk of cyber-attacks, which are increasing in frequency and sophistication and are made by groups and individuals with a wide range of motives and expertise, including criminal groups, “hackers” and others. Cyber-attacks could include the deployment of harmful malware, viruses, worms, denial-of-service attacks, ransomware, phishing, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. Despite our efforts to monitor and safeguard our systems to prevent data compromise, the possibility of a future data compromise cannot be eliminated entirely, and risks associated with intrusion, tampering and theft remain. If our systems were to fail or we are unable to successfully expand the capacity of these systems, or we are unable to integrate new technologies into our existing systems, our operations and financial results could suffer.

We also have outsourced certain elements and functions of our operations, including elements of our information technology infrastructure, to third parties, some of which operate outside the U.S. As a result, we manage many independent vendor relationships with third parties who may or could have access to our confidential information. The size and complexity of our and our vendors' systems make such systems potentially vulnerable to service interruptions and to security breaches from inadvertent or intentional actions by our employees, our partners, our vendors or other third parties, or from attacks by malicious third parties.

The Company and its vendors' information technology operations are spread across multiple, sometimes inconsistent platforms, which pose difficulties in maintaining data integrity across systems. The ever-increasing use and evolution of technology, including cloud-based computing, creates opportunities for the unintentional or improper dissemination or destruction of confidential information stored in the Company's systems.

Any breach of our security measures or the accidental loss, inadvertent disclosure, unapproved dissemination, misappropriation or misuse of trade secrets, proprietary information or other confidential information, whether as a result of theft, fraud, cyber-attacks, hacking, trickery or other forms of deception or any other cause, could enable others to produce competing products, use our proprietary technology or information and/or adversely affect our business position. Further, any such interruption, security breach, loss or disclosure of confidential, proprietary or personal information could result in financial, legal, business and reputational harm to our company and could have a material adverse effect on our business, financial condition, results of operations and cash flows.

The risks related to our global operations may adversely impact our revenues, results of operations and financial condition.

In 2022, approximately 4% of our total revenues were from customers outside the U.S. Some of these sales were to governmental entities and other organizations with extended payment terms. Conducting business internationally, including the sourcing, manufacturing, development, sale and distribution of our products and services across international borders, subjects us to extensive U.S. and foreign governmental trade regulations, such as various anti-bribery laws, including the U.S. Foreign Corrupt Practices Act (FCPA), export control laws, customs and import laws and anti-boycott laws. The FCPA and similar anti-corruption laws in other jurisdictions generally prohibit companies and their intermediaries from making improper payments to government officials for the purpose of obtaining or retaining business. We cannot provide assurance that our internal controls and procedures will always protect us from criminal acts committed by our employees or third parties with whom we work. If we are found liable for violations of the FCPA or other applicable laws and regulations, either due to our own acts or out of inadvertence, or due to the acts or inadvertence of others, we could suffer significant criminal, civil and administrative penalties, including, but not limited to, imprisonment of individuals, fines, denial of export privileges, seizure of shipments, restrictions on certain business activities and exclusion or debarment from government contracting, as well as reputational harm. Also, the failure to comply with applicable legal and regulatory obligations could result in the disruption of our shipping and sales activities.

In addition, some countries where we source, develop, manufacture or sell products are subject to political, economic and/or social instability. Our non-U.S. R&D, manufacturing and sales operations expose us and our employees, representatives, agents and distributors to risks inherent in operating in non-U.S. jurisdictions. For example, we currently perform certain R&D and manufacturing operations in India and plan to expand these operations, including through investment in our manufacturing site in Indore. A disruption in our Indian operations could have a material adverse effect on our business, financial condition, results of operations and cash flows. These risks include, among others:

- the imposition of additional U.S. and non-U.S. governmental controls or regulations;
- the imposition of costly and lengthy new export licensing requirements;
- the imposition of U.S. and/or international sanctions against a country, company, person or entity with whom we do business that would restrict or prohibit continued business with the sanctioned country, company, person or entity;
- economic or political instability or disruptions, including local or regional instability, civil unrest or hostilities, rioting, military activity, terror attacks or armed hostilities;
- disruptions due to natural disasters, earthquakes, cyclones, tornados, typhoons, flooding, droughts, landslides, geological events or severe weather events which may be exacerbated by the effects of climate change;
- disruptions related to COVID-19 or other pandemics;
- changes in duties and tariffs, license obligations and other non-tariff barriers to trade;
- the imposition of new trade restrictions including foreign exchange controls;
- supply disruptions and increases in energy and transportation costs;
- the imposition of restrictions on the activities of foreign agents, representatives and distributors;
- changes in global tax laws and/or the imposition by tax authorities of significant fines, penalties and additional taxes;
- pricing pressure that we may experience internationally;
- fluctuations in foreign currency exchange rates;
- competition from local, regional and international competitors;
- difficulties and costs of staffing and managing foreign operations, including cultural differences and additional employment regulations, union workforce negotiations and potential disputes in the jurisdictions in which we operate;
- difficulties and costs of obtaining and maintaining labs, R&D sites, manufacturing facilities and other locations in which we operate;

- COVID-19 or other outbreaks, epidemics or pandemics as described in the risk factor “Widespread health problems, including the recent global coronavirus, could materially and adversely affect our business” set forth in this report;
- laws and business practices favoring local companies;
- difficulties in enforcing or defending intellectual property rights; and
- exposure to different legal and political standards due to our conducting business in foreign countries.

We also face the risk that some of our competitors have more experience with operations in such countries or with international operations generally and may be able to manage unexpected crises more easily. Furthermore, whether due to language, cultural or other differences, public and other statements that we make may be misinterpreted, misconstrued or taken out of context in different jurisdictions. Moreover, the internal political stability of, or the relationship between, any country or countries where we conduct business operations may deteriorate, including relationships between the U.S. and other countries. Changes in other countries’ economic conditions, product pricing, political stability or the state of relations between any such countries are difficult to predict and could adversely affect our operations, payment and credit terms and our ability to collect foreign receivables. Any such changes could lead to a decline in our profitability and/or adversely impact our ability to do business. Any meaningful deterioration of the political or social stability in and/or diplomatic relations between any countries in which we or our partners and suppliers do business could have a material adverse effect on our business, financial condition, results of operations and cash flows. A substantial slowdown of the global economy, or major national economies, could negatively affect growth in the markets in which we operate. Such a slowdown could result in national governments making significant cuts to their public spending, including national healthcare budgets, or reducing the level of reimbursement they are willing and able to provide to us for our products and, as a result, adversely affect our revenues, financial condition or results of operations. We have little influence over these factors and changes could have a material adverse effect on our business, financial condition, results of operations and cash flows.

We cannot provide assurance that one or more of these factors will not harm our business. Risks associated with our non-U.S. R&D, manufacturing or sales could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Widespread health problems, including the recent global coronavirus, could materially and adversely affect our business.

Public health outbreaks, epidemics or pandemics, such as the coronavirus, could materially and adversely impact our business. For example, the COVID-19 pandemic has resulted in global business and economic disruption and extreme volatility in the financial markets as many jurisdictions have placed restrictions on travel and non-essential business operations and implemented social distancing, shelter-in-place, quarantine and other similar measures for their residents to contain the spread of the virus. In response to these public health directives and orders and in order to provide for the well-being of our workforce around the globe while continuing to safely produce products upon which patients and their healthcare providers rely, we implemented alternative working practices and work-from-home requirements for appropriate employees, inclusive of our Senior Executive Team. We limited international and domestic travel, increased our already-thorough cleaning protocols throughout our facilities and prohibited non-essential visitors from our sites. We also implemented temperature screenings, health questionnaires, social distancing, modified schedules, shift rotation and/or other similar policies at our manufacturing facilities. We have since begun to adjust certain of these practices, reflecting the evolved guidelines from health and other governmental authorities. The effects of COVID-19, including these public health directives and orders and our policies, have had an impact on our business and may in the future materially disrupt our business (including our manufacturing and supply chain operations by significantly reducing our output), negatively impact our productivity and delay our product development programs. COVID-19 contributed to some delays in the completion of our facility in Indore, including delays related to construction and FDA inspections.

Widespread health problems may have significant impacts on third-party arrangements, including those with our manufacturing, supply chain and distribution partners, information technology and other service providers and business partners. For example, there may be significant disruptions in the ability of any or all of these third-party providers to meet their obligations to us on a timely basis, or at all, which may be caused by their own financial or operational difficulties, including any closures of their facilities pursuant to a governmental order or otherwise. Additionally, the supply of goods and services worldwide may be adversely affected as a result of increased pressure on global logistics network infrastructure and capacity or otherwise, which could result in interruptions of supply and/or increased costs based upon inability to obtain, and/or delayed deliveries of, raw materials and/or critical supplies necessary to continue our manufacturing activities and/or those of our third-party suppliers. See the risk factor “Supply chain and other manufacturing disruptions could negatively impact our businesses” for more information.

Due to these disruptions and other factors, including changes in our workforce availability and increased demand for some of our critical care products, our ability to meet our obligations to third-party distribution partners may be negatively impacted. We have delivered, and in the future we or our third-party providers may deliver, notices of the occurrence of *force majeure* or similar events under certain of our third-party contracts, which could result in prolonged commercial disputes and ultimately legal proceedings to enforce contractual performance and/or recover losses. Any such occurrences could result in significant management distraction and use of resources and, in the event of an adverse judgment, could result in significant cash payments. Further, the publicity of any such dispute could harm our reputation and make the negotiation of any replacement contracts more difficult and costly, thereby prolonging the effects of any resulting disruption in our operations. Such disruptions could be acute with respect to certain of our raw material suppliers where we may not have readily accessible alternatives or alternatives may take longer to source than usual. While we attempt, when possible, to mitigate our raw material supply risks through stock management and alternative sourcing strategies, some raw materials are only available from one source. Any of these disruptions could harm our ability to meet consumer demand, including any increase in demand for any of our products, including our critical care products used during a pandemic.

We have experienced, and expect to continue to experience, changes in customer demand as the COVID-19 pandemic continues to evolve, which are difficult to predict. For example, certain of our products that are physician administered, including XIAFLEX®, generally experienced decreased sales volumes during the COVID-19 pandemic due to reduced physician office activity and patient office visits because of the COVID-19 pandemic. While these products have generally been recovering since early 2020, they have at times continued to be impacted by COVID-19-related and, more recently, other market conditions for specialty product office-based procedures, including medical and administrative staff shortages in physicians' offices, reduced physician office activity and lower numbers of in-person patient office visits. The pandemic and other market conditions also created a high backlog of demand for non-elective urology procedures, which has in certain cases reduced the utilization of XIAFLEX® by healthcare providers. Additionally, we believe that concerns by healthcare providers regarding economic uncertainty have impacted purchasing patterns of XIAFLEX®.

Economic crises and increases in unemployment rates resulting from widespread health problems have the potential to significantly reduce individual disposable income, result in lower levels of healthcare insurance coverage and/or depress consumer confidence, any of which could limit the ability of some consumers to purchase certain pharmaceutical products and reduce consumer spend on certain medical procedures in both the short- and medium-term. We are unable to predict the impact that widespread health problems may have going forward on the business, results of operations or financial position of any of our major customers, which could impact each customer to varying degrees and at different times and could ultimately impact our own financial performance. Certain of our competitors may also be better equipped to weather the impact of widespread health problems both domestically and abroad and better able to address changes in customer demand.

Additionally, our product development programs have been, and may continue to be, adversely affected by epidemics, pandemics and other widespread health problems. Public health directives may cause delays, increased costs and additional challenges in our product development programs, including obtaining adequate patient enrollment and successfully bringing product candidates to market. In addition, we may face additional challenges receiving regulatory approvals as previously scheduled dates or anticipated deadlines for action by the FDA on our applications and products in development could be subject to delays beyond our control.

Widespread health problems could increase the magnitude of many of the other risks described herein and have other adverse effects on our operations that we are not able to predict. For example, global economic disruptions and volatility in the financial markets could further depress our ability to obtain or renew insurance on satisfactory terms or at all. Further, we may be required to delay or limit our internal strategies in the short- and medium-term by, for example, redirecting significant resources and management attention away from implementing our strategic priorities or executing opportunistic corporate development transactions.

Any of the risks described herein could also apply in the event of future outbreaks. COVID-19 and other similar outbreaks, epidemics or pandemics could have a material adverse effect on our business, financial condition, results of operations and cash flows and could cause significant volatility in the trading prices of our securities.

Supply chain and other manufacturing disruptions could negatively impact our businesses.

We have experienced increased pressure and infrastructure capacity challenges to our global logistics network. Materials, equipment and labor shortages, shipping, logistics and other delays and other supply chain and manufacturing disruptions, whether due to the evolving effects of the COVID-19 pandemic or otherwise, continue to make it more difficult and costly for us to obtain raw materials, supplies or services from third parties, to manufacture our own products and to pursue clinical development activities. Economic or political instability or disruptions, such as the conflict in Ukraine, could negatively affect our supply chain or increase our costs. If these types of events or disruptions continue to occur, they could have a material adverse effect on our business, financial condition, results of operations and cash flows.

We may be impacted by the effects of climate change and encounter challenges implementing sustainability-related measures.

Climate change resulting from increased concentrations of carbon dioxide and other greenhouse gases in the atmosphere could present risks to our operations, including an adverse impact on global temperatures, weather patterns and the frequency and severity of extreme weather and natural disasters. Severe weather events, natural disasters and other disruptions, such as earthquakes, geological events, hurricanes, cyclones, tornados, typhoons, flooding, droughts, landslides and wildfires, may pose physical risks to our facilities and disrupt the operation of our supply chain. The impacts of the changing climate on water resources may result in water scarcity, limiting our ability to access sufficient high-quality water in certain locations, which may increase operational costs.

Concern over climate change may also result in new or additional legal or regulatory requirements designed to reduce greenhouse gas emissions and/or mitigate the effects of climate change on the environment. If such laws or regulations are more stringent than current legal or regulatory obligations, we may experience disruption in, or an increase in the costs associated with, sourcing, manufacturing and distributing our products, which could have a material adverse effect on our business, financial condition, results of operations and cash flows. We may be unable to successfully implement sustainability-related measures pursuant to our ESG strategy or to adequately respond to increased stakeholder focus on ESG matters including climate change.

Risks Related to Bankruptcy and Our Ordinary Shares

We are subject to risks and uncertainties associated with the Chapter 11 Cases.

The Chapter 11 Cases could have a material adverse effect on our business, financial condition, results of operations and cash flows. So long as the Chapter 11 Cases continue, our senior management may be required to spend a significant amount of time and effort dealing with bankruptcy proceedings instead of focusing on our business operations. The bankruptcy proceedings also may make it more difficult to retain management and the key personnel necessary to the success and growth of our business. In addition, during the period of time we are involved in the Chapter 11 Cases, our customers and suppliers may lose confidence in our ability to restructure our business and may seek to establish alternative commercial relationships.

Other significant risks associated with the Chapter 11 Cases that could have a material adverse effect on our business, financial condition, results of operations and cash flows include or relate to the following, among others:

- our ability to obtain approval from the Bankruptcy Court (as defined below) with respect to motions or other requests made to the Bankruptcy Court in the Chapter 11 Cases, including maintaining control as debtors-in-possession;
- our ability to consummate the Sale or another restructuring transaction, including in light of the currently outstanding objections relating to the Sale and proposed marketing process filed by certain stakeholders in the Chapter 11 Cases;
- the effects of the filing of the Chapter 11 Cases on our business and the interests of various constituents, including our shareholders;
- the high costs of the Chapter 11 Cases and related fees;
- our ability to maintain relationships with suppliers, customers, employees and other third parties as a result of the Chapter 11 Cases;
- Bankruptcy Court rulings in the Chapter 11 Cases as well as the outcome of other pending litigation and the outcome of the Chapter 11 Cases in general;
- the length of time that we will operate with chapter 11 protection and any resulting risk that we will not satisfy the milestones specified in the RSA and in our agreement with our secured lenders with respect to our use of their cash collateral;
- the availability of operating capital during the pendency of the Chapter 11 Cases, including any event that could terminate our right to continued access to the cash collateral of our lenders to use as operating capital;
- third-party motions in the Chapter 11 Cases, which may interfere with our ability to consummate the Sale or another restructuring transaction;
- the impact on our business following the Sale in light of possible changes in our business and its prospects;
- the adequacy of our cash balances at the time of the Sale and our projected exit from the Chapter 11 Cases; and
- our ability to continue as a going concern.

Because of the risks and uncertainties associated with the Chapter 11 Cases, we may not be able to accurately predict or quantify the ultimate impact the Chapter 11 Cases may have on our business, financial condition, results of operations and cash flows, nor can we accurately predict the ultimate impact the Chapter 11 Cases may have on our corporate or capital structure.

Delays in the Chapter 11 Cases may increase the risks of our being unable to consummate the Sale and increase our costs associated with the Chapter 11 Cases.

The RSA contemplates the consummation of the Sale, but there can be no assurance that we will be able to consummate the Sale. A prolonged chapter 11 proceeding could adversely affect our relationships with customers, suppliers and employees, among other parties, which in turn could have a material adverse effect on our business, financial condition, results of operations and cash flows, as well as our ability to continue as a going concern. A weakening of our business, financial condition, results of operations and cash flows could adversely affect our ability to implement the Sale (or any alternative restructuring transaction). If we are unable to consummate the Sale (or an alternative restructuring transaction), we may be forced to liquidate our assets.

The RSA is subject to significant conditions and milestones that may be difficult for us to satisfy.

There are certain material conditions we must satisfy under the RSA, including the timely satisfaction of milestones in the Chapter 11 Cases, which include the consummation of the Sale. Our ability to timely complete such milestones is subject to risks and uncertainties, many of which are beyond our control. Failure to meet such milestones could have a material adverse effect on our business, financial condition, results of operations and cash flows.

If the RSA is terminated, our ability to confirm and consummate the Sale could be materially and adversely affected.

The RSA contains a number of termination events, upon the occurrence of which certain parties to the RSA may terminate the agreement. If the RSA is terminated as to all parties thereto, each of the parties thereto will be released from its obligations in accordance with the terms of the RSA. Such termination may result in the loss of support for the Sale by the parties to the RSA, which could adversely affect our ability to consummate the Sale. If the Sale is not consummated, there can be no assurance that the Chapter 11 Cases would not be converted to chapter 7 liquidation cases or that an alternative restructuring transaction would be as favorable to holders of claims against us as the Sale transaction.

Even if the Sale or an alternative restructuring transaction is consummated, we may not be able to achieve our stated goals or continue as a going concern.

Even if the Sale or an alternative restructuring transaction is consummated, we may continue to face a number of risks, such as changes in economic conditions, changes in our industry, changes in demand for our products and increasing expenses. Some of these risks become more acute when cases under the Bankruptcy Code continue for a protracted period without indication of how or when the cases may be completed. As a result of these risks and others, we cannot guarantee that the Sale or an alternative restructuring transaction will achieve our stated goals or that our business will be able to continue as a going concern.

Furthermore, even if our debts and other liabilities are reduced or discharged through the chapter 11 process, we may need to raise additional funds through public or private debt or equity financing or other various means to fund our business after the completion of the Chapter 11 Cases. Our access to additional financing may be limited, if it is available at all. Therefore, adequate funds may not be available when needed or may not be available on favorable terms, or at all.

Our ability to prosecute the Chapter 11 Cases and consummate the Sale may be contested by third parties with litigation.

Certain of our creditors and other parties in interest may bring litigation against us during the course of the Chapter 11 Cases, the outcome of which is uncertain. Such litigation may prolong the Chapter 11 Cases and may make it difficult for us to reach the contractual milestones for the Chapter 11 Cases within the timeframe set out in the RSA. Failure to meet such milestones could have a material adverse effect on our business, financial condition, results of operations and cash flows.

In certain instances, a chapter 11 case may be converted to a case under chapter 7 of the Bankruptcy Code.

Upon a showing of cause, the Bankruptcy Court may convert the Chapter 11 Cases to cases under chapter 7 of the Bankruptcy Code. In such event, a chapter 7 trustee would be appointed or elected to liquidate our assets for distribution in accordance with the priorities established by the Bankruptcy Code. We believe that liquidation under chapter 7 would diminish recoveries for our creditors because of: (i) the likelihood that the assets would have to be sold or otherwise disposed of in a distressed fashion over a short period of time rather than in a controlled manner and as a going concern; (ii) additional administrative expenses involved in the appointment of a chapter 7 trustee; and (iii) additional expenses and claims, some of which would be entitled to priority, that would be generated during the liquidation and from the rejection of leases and other executory contracts in connection with a cessation of operations.

Termination of our exclusive right to file a chapter 11 plan and the exclusive right to solicit acceptances could result in other parties in interest filing plans of reorganization, which could have less favorable terms than under the Sale transaction or result in significant litigation and expenses.

Following the commencement of the Chapter 11 Cases, we had the exclusive right to file a chapter 11 plan through and including December 14, 2022, and the exclusive right to solicit acceptances of any such plan through February 13, 2023. Deadlines such as these may be extended from time to time by the Bankruptcy Court for cause as permitted by section 1121(d) of the Bankruptcy Code. It is also possible that: (i) parties in interest could seek to shorten or terminate such exclusive plan filing and solicitation periods "for cause" (as permitted by section 1121(d) of the Bankruptcy Code) or seek to oppose any requested extension or (ii) that such periods could expire without extension.

On December 14, 2022, we filed a motion with the Bankruptcy Court seeking extensions of our initial exclusive filing and solicitation periods. Several parties in interest have filed objections to the requested extensions. While certain of these objections have been consensually resolved in principle, others remain outstanding. The Bankruptcy Court hearing on the exclusivity extension motion has been adjourned to an undetermined date, and in the interim, our exclusive periods have been extended to March 20, 2023 and may be subject to further extension based on when the hearing on the exclusivity extension motion is scheduled.

If our exclusive filing and solicitation periods expire or are terminated, other parties in interest will be permitted to file plans of reorganization. There can be no assurances that recoveries under any such plans would be more favorable to creditors than under the Sale or an alternative restructuring transaction. In addition, such plans of reorganization may entail significant litigation and significantly increase the expenses of administration of the Debtors' cases, which could deplete creditor recoveries. Furthermore, if the Bankruptcy Court does not extend the Debtors' exclusive periods, the Ad Hoc First Lien Group (as defined below) could contend that such failure to obtain an extension gives rise to a default under the Cash Collateral Order. If the Ad Hoc First Lien Group seeks to terminate our use of cash collateral, such action could have a material adverse effect on our business, financial condition, results of operations and cash flows.

As a result of the Chapter 11 Cases, our historical financial information may not be indicative of our future performance, which may be volatile.

During the Chapter 11 Cases, we expect our financial results to continue to be volatile as restructuring activities and expenses, potential contract terminations and/or rejections and claims assessments significantly impact our Consolidated Financial Statements. As a result, our historic financial performance is likely not indicative of our financial performance after the Petition Date. In addition, if we emerge from chapter 11, the amounts reported in subsequent periods may materially change relative to historic amounts. We also may be required to adopt fresh start accounting, in which case our assets and liabilities would generally be recorded at fair value as of the fresh start reporting date, which may differ materially from the recorded values of assets and liabilities currently included in our Consolidated Balance Sheets. Our financial results after the application of fresh start accounting could also differ significantly from historic trends.

We may be subject to claims that will not be discharged in the Chapter 11 Cases, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

With certain exceptions, the Bankruptcy Code provides that the confirmation of a plan of reorganization generally discharges a debtor from claims arising prior to consummation of a plan of reorganization. Any claims not ultimately discharged pursuant to a plan of reorganization could be asserted against the reorganized entities and could have a material adverse effect on our business, financial condition, results of operations and cash flows. In addition, if we do not pursue a plan of reorganization following consummation of the Sale, there is a risk that claims against us will not be discharged upon our exit from chapter 11.

If we consummate the Sale with the Stalking Horse Bidder, we may not have sufficient liquidity to implement an orderly wind-down process.

The RSA contemplates a marketing process and auction that will be conducted under the supervision of the Bankruptcy Court. The purchaser pursuant to the auction shall be responsible for, among other things, providing cash for the Wind-Down Amount (as defined below) to fund an orderly wind down process, as further discussed in Note 2. Bankruptcy Proceedings in the Consolidated Financial Statements included in Part IV, Item 15 of this report. The Wind-Down Amount relies on certain assumptions, including a nine-month wind-down process. It also reflects an estimate of anticipated costs to fund various items, such as director fees, professional fees, liquidation proceedings in non-U.S. jurisdictions and other administrative expenses arising after consummation of the Sale. However, there is no guarantee that the assumptions or estimates taken into account in calculating the Wind-Down Amount will result in the provision of sufficient funds to implement an orderly wind-down process.

The pursuit of the Chapter 11 Cases has consumed, and will continue to consume, a substantial portion of the time and attention of our management, which could have a material adverse effect on our business, financial condition, results of operations and cash flows, and could cause us to experience increased levels of employee attrition.

While the Chapter 11 Cases continue, our management will be required to spend a significant amount of time and effort focusing on the Chapter 11 Cases instead of focusing exclusively on our business operations. This diversion of attention could have a material adverse effect on our business, financial condition, results of operations and cash flows, particularly if the Chapter 11 Cases are protracted.

Furthermore, during the pendency of the Chapter 11 Cases, we may experience increased levels of employee attrition and our employees may face considerable distraction and uncertainty. A prolonged period of operating under Bankruptcy Court protection also may make it more difficult to retain management and other key personnel necessary to the success and growth of our business. A loss of key personnel or material erosion of employee morale could adversely affect our business and results of operations. The loss of services of members of our senior management team could also impair our ability to execute our strategy and implement operational initiatives, which would be likely to have a material adverse effect on our business, financial condition, results of operations and cash flows. In addition, the longer the Chapter 11 Cases continue, the more likely it is that vendors and employees will lose confidence in our ability to reorganize our business successfully.

Our current operations and future growth may require significant additional capital, and the amount and terms of our indebtedness could impair our ability to fund our capital requirements. Our current sources of financing may be insufficient to fund our cash requirements through emergence from bankruptcy.

Our business requires substantial capital. We may require additional capital in the event of growth opportunities, unanticipated maintenance requirements or significant departures from our current business plan. Additional financing may not be available on a timely basis or on terms acceptable to us, or at all.

Failure to obtain additional financing, should the need for it develop, could impair our ability to fund capital expenditure requirements and meet debt service requirements and could have a material adverse effect on our business, financial condition, results of operations and cash flows. Further, for the duration of the Chapter 11 Cases, we will be subject to various risks, including but not limited to: (i) the inability to maintain or obtain sufficient financing sources for operations or to fund the Chapter 11 Cases and meet future obligations and (ii) increased legal and/or professional costs associated with the Chapter 11 Cases and our reorganization.

We may be unable to comply with restrictions imposed by the Cash Collateral Order.

The Cash Collateral Order imposes a number of restrictions on us. For example, the Cash Collateral Order requires the Debtors to maintain at least $600.0 million of "liquidity," calculated at the end of each week as unrestricted cash and cash equivalents plus certain specified amounts of restricted cash associated with the TLC Agreement (as defined below). The Cash Collateral Order also requires compliance with variance covenants that compare actual operating disbursements and receipts and capital expenditures to the budgeted amounts set forth in the cash collateral budgets delivered thereunder from time to time pursuant to the terms of the Cash Collateral Order. The Ad Hoc First Lien Group may also contend that the Cash Collateral Order requires the Debtors to obtain extensions to our exclusive plan filing and solicitation periods, as described in more detail herein. Our ability to comply with these provisions may be affected by events beyond our control and our failure to comply could result in an event of default under the Cash Collateral Order, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Aspects of the Chapter 11 Cases limit the flexibility of our management team in running our business.

While we operate our business under supervision by the Bankruptcy Court, we are required to obtain approval by the Bankruptcy Court, and in some cases certain other parties, prior to engaging in activities or transactions outside the ordinary course of business. Bankruptcy Court approval of non-ordinary course activities entails preparation and filing of appropriate motions with the Bankruptcy Court, negotiation with various parties in interest and one or more hearings. Parties in interest may be heard at any Bankruptcy Court hearing and may raise objections with respect to these motions. This process may delay major transactions and limit our ability to respond quickly to opportunities and events in the marketplace. Furthermore, in the event the Bankruptcy Court does not approve a proposed activity or transaction, we would be prevented from engaging in such activities or transactions, even if we believed they would be beneficial. Delays in receiving approvals or failures to receive approvals could have a material adverse effect on our business, financial condition, results of operations and cash flows.

In addition, as noted above, the Cash Collateral Order imposes a number of restrictions on us that may limit the flexibility of our management team in running our business.

We also may become subject to operating covenants that apply to substantially all of our business under the purchase and sale agreement that we anticipate entering into in connection with the Sale. These covenants may require us to operate in the ordinary course of business, to refrain from taking certain enumerated actions and to affirmatively take other enumerated actions. Such covenants may limit the flexibility of our management to respond to various events and circumstances that may arise from time to time, including as a result of the Chapter 11 Cases. If those covenants apply to our business, there can be no assurances that we will be able to obtain appropriate waivers from such covenants as may be necessary or advisable, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

The trading prices of our securities have been volatile, and investments in our securities could decline in value.

The market prices for securities of Endo, and of pharmaceutical companies in general, have been highly volatile and may continue to be highly volatile in the future. For example, in 2022, our ordinary shares were quoted at prices between approximately $0.06 and $3.98 per share. The following factors, in addition to other risk factors described in this section, may have caused and may in the future cause the market value of our securities to fluctuate:

- Developments related to our bankruptcy proceedings and certain related transactions;
- FDA approval or disapproval of any of the drug applications we have submitted;
- the success or failure of our clinical trials;
- the success or failure of our ESG strategy and our ability to respond to increased stakeholder focus on ESG matters including climate change;
- new data or new analyses of older data that raise potential safety or effectiveness issues concerning our approved products;
- product recalls or withdrawals;
- competitors announcing technological innovations or new commercial products;

- introduction of generic, compounded or other substitutes for our products, including the filing of ANDAs with respect to generic versions of our branded products;
- developments concerning our or others' proprietary rights, including patents;
- competitors' publicity regarding actual or potential products under development or other activities affecting our competitors or the industry in general;
- regulatory developments in the U.S. and foreign countries, or announcements relating to these matters;
- period-to-period fluctuations in our financial results;
- new legislation, regulation, administrative guidance or executive orders, or changes in interpretation of existing legislation, regulation, administrative guidance or executive orders, including by virtue of new judicial decisions, that could affect the development, sale or pricing of pharmaceutical products, the number of individuals with access to affordable healthcare, the taxes we pay and/or other factors;
- a determination by a regulatory agency that we are engaging in or have engaged in inappropriate sales or marketing activities, including promoting off-label uses of our products;
- social and political pressure to lower the cost of pharmaceutical products;
- social and political scrutiny over increases in prices of shares of pharmaceutical companies that are perceived to be caused by a strategy of growth through acquisitions;
- litigation against us or others;
- reports of security analysts and rating agencies;
- judgments or settlements or reports of settlement negotiations concerning opioid-related litigation or claims; and
- changes in the political landscape, regulatory environment and international relations, including different policies that may be pursued by the current U.S. presidential administration.

We have no plans to pay regular dividends on our ordinary shares or to conduct ordinary share repurchases.

We currently do not intend to pay any cash dividends in the foreseeable future on our ordinary shares and our ability to do so is restricted during the pendency of the Chapter 11 Cases. Additionally, while our Board of Directors (the Board) has approved a share buyback program (the 2015 Share Buyback Program), of which there is approximately $2.3 billion available as of December 31, 2022, we currently do not intend to conduct ordinary share repurchases in the foreseeable future. Any declaration and payment of future dividends to holders of ordinary shares as well as any repurchase of our ordinary shares under the 2015 Share Buyback Program will be at the sole discretion of the Board and will depend on many factors, including our financial condition, earnings, capital requirements, level of indebtedness, statutory and contractual restrictions applying to the payment of both cash and property dividends or share repurchases (including restrictions imposed by the Bankruptcy Code and related rules and guidelines during the pendency of the Chapter 11 Cases) and other considerations that the Board deems relevant. In addition, our existing debt instruments restrict or prevent us from paying dividends on our ordinary shares and conducting ordinary share repurchases. Agreements governing any future indebtedness, in addition to those governing our current indebtedness, may not permit us to pay dividends on our ordinary shares or conduct ordinary share repurchases.

Our business and operations could be negatively affected by shareholder activism, which could cause us to incur significant expenses, hinder execution of our business strategy and impact our share price.

In recent years, shareholder activism involving corporate governance, strategic direction and operations has become increasingly prevalent. If we become the subject of such shareholder activism, their demands may disrupt our business and divert the attention of our management, employees and Board. Also, we may incur substantial costs, including legal fees and other expenses, related to such activist shareholder matters. Perceived uncertainties resulting from such activist shareholder matters may result in loss of potential business opportunities with our current and potential customers and business partners, be exploited by our competitors and make attracting and retaining qualified personnel more difficult. In addition, such shareholder activism may cause significant fluctuations in our share price based on temporary or speculative market perceptions, uncertainties or other factors that do not necessarily reflect the underlying fundamentals and prospects of our business.

Our ordinary shares are quoted on the over-the-counter market, and thus may have a limited market and lack of liquidity.

The delisting of our ordinary shares from the Nasdaq Global Select Market could result in significantly lower trading volumes and reduced liquidity for investors seeking to buy or sell ordinary shares. Our ordinary shares are currently quoted on the over-the-counter market, which may have an unfavorable impact on our share price and liquidity. The over-the-counter market is a significantly more limited market than the Nasdaq Global Select Market. The quotation of our shares on the over-the-counter market may result in a less liquid market available for existing and potential shareholders to trade our ordinary shares, could further depress the trading price of our ordinary shares and could have a long-term adverse impact on our ability to raise capital in the future. There can be no assurance that there will be an active market for our ordinary shares, either now or in the future, or that shareholders will be able to liquidate their investments or the price at which they may be liquidated. Accordingly, we urge extreme caution with respect to existing and future investments in our equity and other securities.

We believe it is likely that our ordinary shares will continue to decrease in value as a result of the Chapter 11 Cases.

We have a significant amount of indebtedness that is senior to our ordinary shares in our capital structure. Our existing ordinary shares have substantially decreased in value leading up to and during the Chapter 11 Cases. The proposed Sale transaction to the Stalking Horse Bidder does not contemplate the distribution of any value with respect to our shares, and we do not foresee a market for our existing ordinary shares after any emergence from the Chapter 11 Cases. Accordingly, any trading in our ordinary shares during the pendency of the Chapter 11 Cases is highly speculative and poses substantial risks to purchasers of our ordinary shares.

Litigation and Liability Related Risks

We are regularly the subject of material legal proceedings, including significant lawsuits, product liability claims, governmental investigations and product recalls, any of which could have a material adverse effect on our company.

Our business exposes us to significant potential risks from lawsuits and other material legal proceedings including, but not limited to, matters associated with the testing, manufacturing, marketing, sale and use of our products. Some plaintiffs have received substantial damage awards against or entered into significant settlements with healthcare companies based upon various legal theories including, without limitation, claims for injuries allegedly caused by the use of their products. A number of legal proceedings that we are currently subject to have the potential to result in significant monetary and other damages for which we could be liable. As further described herein, some of these cases are at advanced procedural stages and are scheduled for trial in the near future. We have been, are currently and expect to continue to be subject to various lawsuits, product liability claims, other material legal proceedings, governmental investigations and/or product recalls, any of which could have a material adverse effect on our company.

As further discussed in Note 2. Bankruptcy Proceedings and Note 16. Commitments and Contingencies in the Consolidated Financial Statements included in Part IV, Item 15 of this report, on the Petition Date, the Debtors filed voluntary petitions for relief under the Bankruptcy Code. Under the Bankruptcy Code, third-party actions to collect pre-petition indebtedness owed by the Debtors, as well as most litigation pending against the Debtors as of the Petition Date, are generally subject to an automatic stay. However, under the Bankruptcy Code, certain legal proceedings, such as those involving the assertion of a governmental entity's police or regulatory powers, may not be subject to the automatic stay and may continue unless otherwise ordered by the Bankruptcy Court. As a result, some proceedings may continue (or certain parties may attempt to argue that such proceedings should continue) notwithstanding the automatic stay. It is possible that legal proceedings such as those described herein and/or other matters could in the future cause us to take one or more additional significant corporate transactions or other remedial measures, including on a preventative or proactive basis.

As an example of our legal proceedings, we, as well as various other manufacturers, distributors, pharmacies and/or others, are the subject of numerous lawsuits consisting of cases filed by or on behalf of a wide variety of plaintiffs asserting claims relating to the defendants' alleged sales, marketing and/or distribution practices with respect to prescription opioid medications. In these cases, plaintiffs seek various remedies including, without limitation, declaratory and/or injunctive relief; compensatory, punitive and/or treble damages; restitution, disgorgement, civil penalties, abatement, attorneys' fees, costs and/or other relief. Notwithstanding any relief that may be available as a result of our bankruptcy proceedings, it is possible that our legal proceedings, including those relating to opioid claims, could have a material adverse effect on our business, financial condition, results of operations and cash flows, including in the short term. Refer to Note 16. Commitments and Contingencies in the Consolidated Financial Statements included in Part IV, Item 15 of this report for more information.

As a result of the Chapter 11 Cases and the associated automatic stay, we are no longer actively pursuing our prior integrated settlement and litigation strategy to seek resolution of unsettled cases that have been stayed. Nevertheless, at any given time, we may be engaged in settlement or similar discussions regarding various legal matters including those that arise in connection with the Chapter 11 Cases; however, settlement demands and discussions often involve significant monetary and other remedies and there can be no assurance that we will receive settlement offers that are on terms that we consider reasonable under the circumstances or indicative of the merits or potential outcome of any court proceeding with respect to the underlying claims.

In the past, we have made the decision to settle some claims even though we believe we had meritorious defenses because of the significant legal and other costs that would have been required to defend such claims. To the extent that any litigation arises or proceeds during the pendency of the Chapter 11 Cases, there can be no assurance that settlement opportunities will continue to be available generally, or be consistent with our historic experience, or that we will not settle additional claims even if we believe we have meritorious defenses. Even where settlement agreements have been reached, in certain instances they are subject to conditions and contingencies, including but not limited to participation thresholds and approval of the Bankruptcy Court during the pendency of the Chapter 11 Cases, which may be outside of our control and may not come to pass. In addition, there can be no assurance of the impact of any settlement agreement on existing or future claims.

Awards against or settlements by us or our competitors could incentivize parties to bring additional claims against us or increase settlement demands against us. In addition to the risks of direct expenditures for defense costs, settlements and/or judgments in connection with various claims, proceedings and investigations, there is a possibility of loss of revenues, injunctions and disruption of business. Additionally, we have received, and may continue to receive, claims or requests for indemnification from other persons or entities named in or subject to discovery in various lawsuits or other legal proceedings, including certain of our customers.

We and other manufacturers of prescription opioid medications have been, and will likely continue to be, subject to negative publicity and press, which could harm our brand and the demand for our products.

Our current and former products may cause or appear to cause serious adverse side effects or potentially dangerous drug interactions if misused or improperly prescribed or as a result of faulty surgical technique. We are subject to various risks associated with having operated a medical device manufacturing business, including potential and actual product liability claims for defective or allegedly defective goods and increased government scrutiny and/or potential claims regarding the marketing of medical devices. For example, we and certain other manufacturers have been named as defendants in multiple lawsuits in various federal and state courts alleging personal injury resulting from the use of transvaginal surgical mesh products designed to treat pelvic organ prolapse (POP) and stress urinary incontinence (SUI). The FDA held a public advisory committee meeting in February 2019 during which the members of the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee discussed and made recommendations regarding the safety and effectiveness of surgical mesh to treat POP. In April 2019, following the meeting, the FDA ordered that the manufacturers of all remaining surgical mesh products indicated for the transvaginal repair of POP cease selling and distributing their products in the U.S. effective immediately. Although we have not sold transvaginal surgical mesh products since March 2016, it is possible that the FDA's order and any additional FDA actions based on the outcome of the advisory committee meeting could result in additional litigation against the Company or the expansion of ongoing litigation against the Company. See Note 16. Commitments and Contingencies in the Consolidated Financial Statements included in Part IV, Item 15 of this report for more information.

Any failure to effectively identify, analyze, report and protect adverse event data and/or to fully comply with relevant laws, rules and regulations around adverse event reporting could expose the Company to legal proceedings, penalties, fines and/or reputational damage. As a result of our ongoing bankruptcy proceedings, we could see an increase in the number of adverse events reported, which could increase costs and have other negative impacts.

In addition, in the age of social media, plaintiffs' attorneys have a wide variety of tools to advertise their services and solicit new clients for litigation, including using judgments and settlements obtained in litigation against us or other pharmaceutical companies as an advertising tool. For these or other reasons, any product liability or other litigation in which we are a defendant could have a larger number of plaintiffs than such actions have seen historically and we could also see an increase in the number of cases filed against us because of the increasing use of widespread and media-varied advertising. This could also complicate any settlement discussions we may be engaged in. Furthermore, a ruling against other pharmaceutical companies in product liability or other litigation, or any related settlement, in which we are not a defendant could have a negative impact on pending litigation where we are a defendant.

In addition, in certain circumstances, such as in the case of products that do not meet approved specifications or which subsequent data demonstrate may be unsafe, ineffective or misused, it may be necessary for us to initiate voluntary or mandatory recalls or withdraw such products from the market. Any such recall or withdrawal could result in adverse publicity, costs connected to the recall and loss of revenue. Adverse publicity could also result in an increased number of additional product liability claims, whether or not these claims have a basis in scientific fact. See the risk factor "Public concern around the abuse of opioids or other products including, without limitation, law enforcement concerns over diversion or marketing practices, regulatory efforts to combat abuse and litigation could result in costs to our business and damage our reputation" for more information.

If we are found liable in any lawsuits, including the legal proceedings related to our sale, marketing and/or distribution of prescription opioid medications, product liability claims or actions related to our sales, marketing or pricing practices or if we are subject to governmental investigations or product recalls, it could result in the imposition of material damages, including punitive damages, fines, reputational harm, civil lawsuits, criminal penalties, interruptions of business, modification of business practices, equitable remedies and other sanctions against us or our personnel as well as significant legal and other costs. At any given time, we may be engaged in settlement or similar discussions, and we may voluntarily settle claims even if we believe that we have meritorious defenses because of the significant legal and other costs that may be required to defend such claims. Any judgments, claims, settlements and related costs could be well in excess of any applicable insurance or accruals. As a result, we may experience significant negative impacts on our results of operations or financial condition. To satisfy judgments or settlements or to pursue certain appeals, we may need to seek financing or bonding, which may not be available on terms acceptable to us, or at all, when required, particularly given the nature and amount of the claims against us. Judgments against us could also cause defaults under our debt agreements (which could result in cross-defaults or cross-accelerations in other agreements) and/or restrictions on product use or business practices and we could incur losses as a result. Any of the risks above could have a material adverse effect on our business, financial condition, results of operations and cash flows.

In July 2021, a court in one legal action issued an order granting a default judgment on liability against Endo Pharmaceuticals Inc. (EPI) and Endo Health Solutions Inc. (EHSI) and awarding the plaintiffs fees and costs relating to certain alleged discovery issues in an opioid-related lawsuit. Although we settled that matter, plaintiffs have from time to time sought similar relief and may do so in the future. Any future default judgments or other sanctions relating to discovery matters could result in the imposition of material damages or other costs.

The August 16, 2022 bankruptcy filings by the Debtors constituted an event of default that accelerated our obligations under substantially all of our then-outstanding debt instruments. However, section 362 of the Bankruptcy Code stays creditors from taking any action to enforce the related financial obligations and creditors' rights of enforcement in respect of the debt instruments are subject to the applicable provisions of the Bankruptcy Code. Refer to Note 15. Debt in the Consolidated Financial Statements included in Part IV, Item 15 of this report for additional information.

See Note 16. Commitments and Contingencies in the Consolidated Financial Statements included in Part IV, Item 15 of this report for further discussion of the foregoing and other material legal proceedings.

We may not have and may be unable to obtain or maintain insurance adequate to cover potential liabilities.

We may not have and may be unable to obtain or maintain insurance on acceptable terms or with adequate coverage against potential liabilities or other losses, including costs, judgments, settlements and other liabilities incurred in connection with current or future legal proceedings, regardless of the success or failure of the claim. For example, we do not have insurance sufficient to satisfy all of the opioid claims that have been made against us. We also generally no longer have product liability insurance to cover claims in connection with the mesh-related litigation described herein. Additionally, we may be limited by the surviving insurance policies of acquired entities, which may not be adequate to cover potential liabilities or other losses. Even where claims are submitted to insurance carriers for defense and indemnity, there can be no assurance that the claims will be covered by insurance or that the indemnitors or insurers will remain financially viable or will not challenge our right to reimbursement in whole or in part. The failure to generate sufficient cash flow or to obtain other financing could affect our ability to pay amounts due under those liabilities not covered by insurance. Additionally, the nature of our business, the legal proceedings to which we are exposed and any losses we suffer may increase the cost of insurance, which could impact our decisions regarding our insurance programs.

Public concern around the abuse of opioids or other products including, without limitation, law enforcement concerns over diversion or marketing practices, regulatory efforts to combat abuse and litigation could result in costs to our business and damage our reputation.

Media stories regarding drug abuse and diversion, including the abuse and diversion of prescription opioid medications and other controlled substances, are commonplace and have included the Company. Aggressive enforcement and unfavorable publicity regarding, for example, the use or misuse of opioids, the limitations of abuse-deterrent formulations, the ability of abusers to discover previously unknown ways to abuse our products, public inquiries and investigations into drug abuse or litigation or regulatory or enforcement activity regarding sales, marketing, distribution or storage of opioids could have a material adverse effect on our reputation, on the results of litigation and on our ability to attract or maintain relationships with third-party partners, including suppliers, vendors, advisors, distributors, manufacturers, collaboration partners, administrators and agents. As a result of the timing and schedule of certain legal proceedings against us, we will likely be subject to additional press for the foreseeable future.

Manufacturers of prescription opioid medications have been the subject of significant civil and criminal investigatory and enforcement actions even in cases where such medications have received approval from the FDA or similar regulatory authorities. Numerous governmental and private persons and entities are pursuing litigation against opioid manufacturers, including us, as well as distributors and others, asserting alleged violations of various laws and regulations relating to opioids and/or other prescription medicines, relying on common law theories, and seeking to hold the defendants accountable for, among other things, societal costs associated with the misuse and abuse of prescription opioid medications as well as non-prescription opioids. There is a risk we will be subject to similar investigations, enforcement actions or litigations in the future, that we will suffer adverse decisions or verdicts of substantial amounts or that we will enter into monetary settlements. Notwithstanding any relief that may be available as a result of our bankruptcy proceedings, it is possible that our legal proceedings, including those relating to opioid claims, could have a material adverse effect on our business, financial condition, results of operations and cash flows. See Note 16. Commitments and Contingencies in the Consolidated Financial Statements included in Part IV, Item 15 of this report for more information.

There have been proposals in certain legislatures to restrict the ability to compromise or release liability of certain parties in such cases, and we cannot assure you whether any such proposals will be made or adopted in the future or predict how any such proposals may affect the Company.

Regulatory actions at the federal, state and local level may seek to limit or restrict the manufacturing, distribution or sale of opioids, both directly and indirectly, and/or to impose novel policy or regulatory mechanisms regarding the distribution or sales of opioids. For example, in April 2019, New York enacted an excise tax on opioids. See the risk factor "Our business and financial condition may be adversely affected by existing or future legislation and regulations" for more information.

Various government entities, including the U.S. Congress, state legislatures or other policy-making bodies in the U.S. or elsewhere have held hearings, conducted investigations and/or issued reports calling attention to opioid misuse and abuse, and some have mentioned or criticized the role of manufacturers, including us, in supplying or marketing opioid medications or failing to take adequate steps to detect or report suspicious orders or to prevent abuse and diversion. Press organizations have reported and likely will continue to report on these issues, and such reporting has and may further result in adverse publicity which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Financial and Liquidity Related Risks

Our ability to fund our operations, maintain adequate liquidity and meet our financing obligations is reliant on our operations, which are subject to significant risks and uncertainties.

We rely on cash from operations as well as access to the financial markets to fund our operations, maintain liquidity and meet our financial obligations. Our operations are subject to many significant risks and uncertainties, including those related to generic competition and legal challenges that could impact our key products, outstanding and future legal proceedings and governmental investigations, including those related to our sale, marketing and/or distribution of prescription opioid medications, and others. Any negative development or outcome in connection with any or all of these risks and uncertainties could result in significant consequences, including one or more of the following:

- causing a substantial portion of our cash flows from operations to be dedicated to the payment of legal or related expenses and therefore unavailable for other purposes, including the payment of principal and interest on our indebtedness, our operations, capital expenditures and future business opportunities;
- limiting our ability to adjust to changing market conditions, causing us to be more vulnerable to periods of negative or slow growth in the general economy or in our business, causing us to be unable to carry out capital spending that is important to our growth and placing us at a competitive disadvantage;
- limiting our ability to attract and retain key personnel;
- causing us to be unable to maintain compliance with or making it more difficult for us to satisfy our financial obligations under certain of our outstanding debt obligations, causing a downgrade of our debt and long-term corporate ratings (which could increase our cost of capital) and exposing us to potential events of default (if not cured or waived) under financial and operating covenants contained in our or our subsidiaries' outstanding indebtedness;
- limiting our ability to incur additional borrowings under the covenants in our then-existing facilities or to obtain additional debt or equity financing for working capital, capital expenditures, business development, debt service requirements, acquisitions or general corporate or other purposes, or to refinance our indebtedness; and/or
- causing a significant reduction in our short-term and long-term revenues and/or otherwise causing us to be unable to fund our operations and liquidity needs, such as future capital expenditures and payment of our indebtedness.

These risks have been and are likely to continue to be exacerbated by our ongoing bankruptcy proceedings and the corresponding event of default on our existing debt instruments, as further discussed herein.

We have significant goodwill and other intangible assets. Consequently, potential impairments of goodwill and other intangibles may significantly impact our profitability.

Goodwill and other intangibles represent a significant portion of our assets. As of December 31, 2022 and 2021, goodwill and other intangibles comprised approximately 54% and 63%, respectively, of our total assets. Goodwill and other indefinite-lived intangible assets are subject to impairment tests at least annually. Additionally, impairment tests must be performed for certain assets whenever events or changes in circumstances indicate such assets' carrying amounts may not be recoverable.

For the years ended December 31, 2022, 2021 and 2020, we recorded asset impairment charges of $2.1 billion, $0.4 billion and $0.1 billion, respectively, which related primarily to goodwill and other intangible assets. Refer to Note 11. Goodwill and Other Intangibles in the Consolidated Financial Statements included in Part IV, Item 15 of this report for examples and a discussion of material impairment tests and impairment charges during the years ended December 31, 2022, 2021 and 2020. The procedures and assumptions used in our goodwill and other intangible assets impairment testing are discussed in Part II, Item 7 of this report "Management's Discussion and Analysis of Financial Condition and Results of Operations" under the caption "CRITICAL ACCOUNTING ESTIMATES" and in Note 11. Goodwill and Other Intangibles in the Consolidated Financial Statements included in Part IV, Item 15 of this report.

Events giving rise to asset impairments are an inherent risk in the pharmaceutical industry and often cannot be predicted. As a result of the significance of goodwill and other intangible assets, our results of operations and financial position in future periods could be negatively impacted should additional impairments of our goodwill or other intangible assets occur. For additional discussion, refer to Item 7 of this report "Management's Discussion and Analysis of Financial Condition and Results of Operations" under the caption "CRITICAL ACCOUNTING ESTIMATES."

We have a substantial amount of indebtedness which could adversely affect our financial position and prevent us from fulfilling our obligations under such indebtedness, which may require us to refinance all or part of our then-outstanding indebtedness. Any refinancing of this substantial indebtedness could be at significantly higher interest rates. Additionally, we have a significant amount of floating rate indebtedness and an increase in interest rates would increase the cost of servicing our indebtedness. Despite our current level of indebtedness, we may still be able to incur substantially more indebtedness and increase the associated risks.

We currently have a substantial amount of indebtedness. As of December 31, 2022, we have total debt of approximately $8.1 billion in aggregate contractual principal amount. Our substantial indebtedness may:

- make it difficult for us to satisfy our financial obligations, including making any applicable scheduled principal, interest and/or adequate protection payments on our indebtedness as further discussed herein;
- limit our ability to borrow additional funds for working capital, capital expenditures, acquisitions or other general business purposes;
- limit our ability to use our cash flow or obtain additional financing for future working capital, capital expenditures, acquisitions or other general business purposes;
- limit our ability to incur judgments above certain thresholds;
- expose us to the risk of rising interest rates with respect to the borrowings under our variable rate indebtedness;
- require us to use a substantial portion of our cash on hand and/or from future operations to make debt service payments;
- limit our flexibility to plan for, or react to, changes in our business and industry;
- place us at a competitive disadvantage compared to our less leveraged competitors; and
- increase our vulnerability to the impact of adverse economic and industry conditions, such as those resulting from the COVID-19 pandemic, which may further limit our ability to satisfy our financial obligations.

If we are unable to pay amounts due under our outstanding indebtedness or to fund other liquidity needs, such as future capital expenditures or contingent liabilities as a result of adverse business developments, including expenses related to our ongoing and future legal proceedings and governmental investigations, decreased revenues or increased costs and expenses related to the impact of COVID-19 on our business, as well as increased pricing pressures or otherwise, we may be required to refinance all or part of our then-existing indebtedness, sell assets, reduce or delay capital expenditures or seek to raise additional capital. Any of these factors could have a material adverse effect on our business, financial condition, results of operations and cash flows.

These risks have been and are likely to continue to be exacerbated by our ongoing bankruptcy proceedings and the corresponding event of default on our existing debt instruments, as further discussed herein. To the extent we are required or choose to seek third-party financing in the future, there can be no assurance that we would be able to obtain any such required financing on a timely basis or at all, particularly in light of our ongoing bankruptcy proceedings and the corresponding event of default on our existing debt instruments. Additionally, any future financing arrangements could include terms that are not commercially beneficial to us, which could further restrict our operations and exacerbate any impact on our results of operations and liquidity that may result from any of the factors described herein or other factors.

At December 31, 2022, approximately $2.0 billion and $0.3 billion of principal amounts outstanding under the Term Loan Facility (as defined below) and the Revolving Credit Facility (as defined below), respectively, bear interest and/or adequate protection payments at variable rates that are affected by benchmark interest rates. Additionally, the amounts of interest and/or adequate protection payments we are required to make on our various debt instruments are subject to changes based on contractual terms set forth in the applicable agreements and/or court orders. Recent increases in benchmark interest rates and certain other developments, including those related to our bankruptcy proceedings, have resulted in increases in the rates used to calculate the interest and/or adequate protection payments we are required to make, and such rates could further increase in future periods. Any future borrowings could also be subject to such risks.

We may not realize the anticipated benefits from our strategic actions.

We continuously seek to optimize our operations and increase our overall efficiency through strategic actions. These actions may involve decisions to exit manufacturing or research sites, transfer the manufacture of products to other internal and external sites within our manufacturing network and simplify business process activities. For example, we announced plans in November 2020 to optimize our retail generics business cost structure, transfer certain transaction processing activities to third-party global business process service providers and further integrate our commercial, operations and research and development functions. There can be no assurance that we will achieve the benefits and savings of actions such as these in the expected amounts and/or with the expected timing, if at all. We will also incur certain charges in connection with such actions and future costs could also be incurred. It is also possible that charges and cash expenditures associated with such actions could be higher than estimated. Any of these risks could ultimately have a material adverse effect on our business, financial condition, results of operations and cash flows.

Legal and Regulatory Related Risks

Agreements between branded pharmaceutical companies and generic pharmaceutical companies are facing increased government scrutiny and we may be subject to additional investigations or litigation.

We are and may in the future be involved in patent litigations in which generic companies challenge the validity or enforceability of our products' listed patents and/or the applicability of these patents to the generic applicant's products. Likewise, we are and may in the future be involved in patent litigations in which we challenge the validity or enforceability of innovator companies' listed patents and/or their applicability to our generic products. Therefore, settling patent litigations has been and is likely to continue to be part of our business. Parties to such settlement agreements in the U.S., including us, are required by law to file them with the U.S. Federal Trade Commission (FTC) and the Antitrust Division of the DOJ for review. In some instances, the FTC has brought actions against brand and generic companies that have entered into such agreements, alleging that they violate antitrust laws. Even in the absence of an FTC challenge, other governmental or private litigants may assert antitrust or other claims relating to such agreements. We may receive formal or informal requests from the FTC or other governmental entities for information about any such settlement agreement we enter into or about other matters, and there is a risk that the FTC or other governmental or private litigants may commence an action against us alleging violation of antitrust laws or other claims. For example, in December 2021, in response to a citizen petition filed on behalf of PSP LLC regarding vasopressin ANDA products referencing VASOSTRICT®, the FDA denied the petition and stated that it intended to refer the matter to the FTC.

The U.S. Supreme Court, in *FTC v. Actavis*, determined that patent settlement agreements between generic and brand companies should be evaluated under the rule of reason, but provided limited guidance beyond the selection of this standard. Because the U.S. Supreme Court did not articulate the full range of criteria upon which a determination of the legality of such settlements would be based, or provide guidance on the precise circumstances under which such settlements would qualify as legal, there has been and may continue to be extensive litigation over what constitutes a reasonable and lawful patent settlement between a brand and generic company. The Company and/or its subsidiaries have been named in several such lawsuits. For example, beginning in May 2018, multiple complaints were filed in the U.S. District Court for the Southern District of New York against PPI, EPI and/or us, as well as other pharmaceutical companies, alleging violations of antitrust law arising out of the settlement of certain patent litigation concerning the generic version of Exforge® (amlodipine/valsartan). See Note 16. Commitments and Contingencies in the Consolidated Financial Statements included in Part IV, Item 15 of this report for more information.

There have been federal and state legislative efforts to overturn the *FTC v. Actavis* decision and make certain terms in patent settlement agreements *per se* unlawful. For example, some members of the U.S. Congress have proposed legislation that would limit the types of settlement agreements generic manufacturers and brand companies can enter into. The state of California enacted legislation, effective January 1, 2020, that deems a settlement of a patent infringement claim to be presumptively anticompetitive and allows the California Attorney General to seek monetary penalties if a generic company receives anything of value from the branded company and the generic company agrees to delay research and development, manufacturing, marketing or sales of the generic product for any period of time. The California law carves out from the definition of "anything of value" certain types of settlement terms and it allows the settling parties to rebut the presumption of anticompetitive harm.

We are subject to various laws and regulations pertaining to the marketing of our products and services.

The marketing and pricing of our products and services, including product promotion, educational activities, support of continuing medical education programs and other interactions with healthcare professionals, are governed by various laws and regulations, including FDA regulations and the U.S. federal Anti-Kickback Statute. Additionally, many states have adopted laws similar to the Anti-Kickback Statute, without identical exceptions or exemptions. Some of these state prohibitions apply to referral of patients for healthcare items or services reimbursed by any third-party payer, not only the Medicare and Medicaid programs. Any such regulations or requirements could be difficult and expensive for us to comply with, could delay our introduction of new products and could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Sanctions for violating these laws include criminal penalties and civil sanctions and possible exclusion from federally funded healthcare programs such as Medicare and Medicaid, as well as potential liability under the FCA and applicable state false claims acts. There can be no assurance that our practices will not be challenged under these laws in the future, that changes in these laws or interpretation of these laws would not give rise to new challenges of our practices or that any such challenge would not have a material adverse effect on our business, financial condition, results of operations and cash flows. For example, in December 2021, the Attorney General of Texas announced an investigation of EPI and AbbVie Inc. under the Texas Deceptive Trade Practices Act for allegedly advertising and promoting hormone (puberty) blockers for unapproved uses without disclosing potential risks. Law enforcement agencies sometimes initiate investigations into sales, marketing and/or pricing practices based on preliminary information or evidence, and such investigations can be and often are closed without any enforcement action. Nevertheless, these types of investigations and any related litigation can result in: (i) large expenditures of cash for legal fees, payment of penalties and compliance activities; (ii) limitations on operations; (iii) diversion of management resources; (iv) injury to our reputation; and (v) decreased demand for our products.

The FFDCA and FDA regulations and guidance restrict the ability of healthcare companies, such as our company, to communicate with patients, physicians and other third parties about uses of prescription pharmaceuticals or devices that are not cleared or approved by the FDA, which are commonly referred to as "off-label" uses. Prohibitions on the promotion of off-label uses and against promotional practices deemed false or misleading are actively enforced by various parties at both the federal and state levels. A company that is found to have improperly promoted its products under these laws may be subject to significant liability, such as significant administrative, civil and criminal sanctions including, but not limited to, significant civil damages, criminal fines and exclusion from participation in Medicare, Medicaid and other federal healthcare programs. Applicable laws governing product promotion also provide for administrative, civil and criminal liability for individuals, including, in some circumstances, potential strict vicarious liability. Conduct giving rise to such liability could also form the basis for private civil litigation by third-party payers or other persons allegedly harmed by such conduct.

We have established and implemented a corporate compliance program designed to prevent, detect and correct violations of state and federal healthcare laws, including laws related to advertising and promotion of our products. Nonetheless, governmental agencies or private parties may take the position that we are not in compliance with such requirements and, if such non-compliance is proven, the Company and, in some cases, individual employees, may be subject to significant liability, including the aforementioned administrative, civil and criminal sanctions.

In February 2014, EPI entered into a Deferred Prosecution Agreement and a Corporate Integrity Agreement (CIA) with HHS to resolve allegations regarding the promotion of LIDODERM®. In March 2013, our subsidiary Par Pharmaceutical Companies, Inc. (PPCI) entered into a CIA and plea agreement with the DOJ to resolve allegations regarding the promotion of MEGACE® ES, which was subsequently subsumed by EPI's CIA. Those agreements placed certain obligations on us related to the marketing of our pharmaceutical products and our healthcare regulatory compliance program, including reporting requirements to the U.S. government, detailed requirements for our compliance program, code of conduct and policies and procedures and the requirement to engage an Independent Review Organization. We implemented procedures and practices to comply with the CIAs, including the engagement of an Independent Review Organization. In February 2020, Endo was notified that it had satisfied its CIA requirements and the 5-year term of Endo's CIA has now concluded.

The pharmaceutical industry is heavily regulated, which creates uncertainty about our ability to bring new products to market and imposes substantial compliance costs on our business, including withdrawal or suspension of existing products.

Governmental authorities, including without limitation the FDA, impose substantial requirements on the development, manufacture, holding, labeling, marketing, advertising, promotion, distribution and sale of therapeutic pharmaceutical products. See "Governmental Regulation" in Part I, Item 1.

Regulatory approvals for the sale of any new product candidate may require preclinical studies and clinical trials that such product candidate is safe and effective for its intended use. Preclinical and clinical studies may fail to demonstrate the safety and effectiveness of a product candidate. Likewise, we may not be able to demonstrate through clinical trials that a product candidate's therapeutic benefits outweigh its risks. Even promising results from preclinical and early clinical studies do not always accurately predict results in later, large-scale trials. A failure to demonstrate safety and efficacy would result in our failure to obtain regulatory approvals.

Clinical trials can be delayed for reasons outside of our control, which can lead to increased development costs and delays in regulatory approval. It is possible that regulators, independent data monitoring committees, institutional review boards, safety committees, ethics committees and/or other third parties may request or require that we suspend or terminate our clinical trials for various reasons, including, among others, noncompliance with regulatory requirements, unforeseen safety issues or adverse side effects or failure to demonstrate a benefit from using our product candidates. There is substantial competition to enroll patients in clinical trials, and such competition has delayed clinical development of our products in the past. For example, patients could enroll in clinical trials more slowly than expected or could drop out before or during clinical trials. In addition, we may rely on collaboration partners that may control or make changes in trial protocol and design enhancements, or encounter clinical trial compliance-related issues, which may also delay clinical trials. Product supplies may be delayed or insufficient to treat the patients participating in the clinical trials, and manufacturers or suppliers may not meet the requirements of the FDA or foreign regulatory authorities, such as those relating to cGMP.

Compliance with clinical trial requirements and cGMP regulations requires significant expenditures and the dedication of substantial resources. The FDA may place a hold on a clinical trial and may cause a suspension or withdrawal of product approvals if regulatory standards are not maintained. In the event an approved manufacturing facility for a particular drug is required by the FDA to curtail or cease operations, or otherwise becomes inoperable, or a third-party contract manufacturing facility faces manufacturing problems, obtaining the required FDA authorization to manufacture at the same or a different manufacturing site could result in production delays, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Additional delays may result if an FDA advisory committee or other regulatory authority recommends non-approval or restrictions on approval. Although the FDA is not required to follow the recommendations of its advisory committees, it usually does. A negative advisory committee meeting could signal a lower likelihood of approval, although the FDA may still end up approving our application. Regardless of an advisory committee meeting outcome or the FDA's final approval decision, public presentation of our data may shed positive or negative light on our application.

We may seek FDA approval for certain unapproved marketed products through the 505(b)(2) regulatory pathway. See "Governmental Regulation" in Part I, Item 1. Even if we receive approval for an NDA under section 505(b)(2) of the FFDCA, the FDA may not take timely enforcement action against companies marketing unapproved versions of the product; therefore, we cannot be sure that that we will receive the benefit of any de facto exclusive marketing period or that we will fully recoup the expenses incurred to obtain an approval. In addition, certain competitors and others have objected to the FDA's interpretation of Section 505(b)(2). If the FDA's interpretation of Section 505(b)(2) is successfully challenged, this could delay or even prevent the FDA from approving any NDA that we submit under Section 505(b)(2).

The ANDA approval process for a new product varies in time, generally requiring a minimum of 10 months following submission of the ANDA to the FDA, but could also take several years from the date of application. The timing for the ANDA approval process for generic products is difficult to estimate and can vary significantly. ANDA approvals, if granted, may not include all uses (known as indications) for which a company may seek to market a product.

The submission of an NDA, Supplemental New Drug Application, ANDA, BLA or sBLA to the FDA with supporting clinical safety and efficacy data does not guarantee that the FDA will grant approval to market the product. Meeting the FDA's regulatory requirements to obtain approval to market a drug product, which vary substantially based on the type, complexity and novelty of the product candidate, typically takes years, if approved at all, and is subject to uncertainty. The FDA or foreign regulatory authorities may not agree with our assessment of the clinical data or they may interpret it differently. Such regulatory authorities may require additional or expanded clinical trials. Any approval by regulatory agencies may subject the marketing of our products to certain limits on indicated use. For example, regulatory authorities may approve any of our product candidates for fewer or more limited indications than we may request, may grant approval contingent on conditions such as the performance and results of costly post-marketing clinical trials or REMS or may approve a product candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. Additionally, reimbursement by government payers or other payers may not be approved at the price we intend to charge for our products. Any limitation on use imposed by the FDA or delay in or failure to obtain FDA approvals or clearances of products developed by us would adversely affect the marketing of these products and our ability to generate product revenue. We could also be at risk for the value of any capitalized pre-launch inventories related to products under development. These factors could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Once a product is approved or cleared for marketing, failure to comply with applicable regulatory requirements can result in, among other things, suspensions or withdrawals of approvals or clearances; seizures or recalls of products; injunctions against the manufacture, holding, distribution, marketing and sale of a product; and civil and criminal sanctions. For example, any failure to effectively identify, analyze, report and protect adverse event data and/or to fully comply with relevant laws, rules and regulations around adverse event reporting could expose the Company to legal proceedings, penalties, fines and reputational damage. Furthermore, changes in existing regulations or the adoption of new regulations could prevent us from obtaining, or affect the timing of, future regulatory approvals or clearances. Meeting regulatory requirements and evolving government standards may delay marketing of our new products for a considerable period of time, impose costly procedures upon our activities and result in a competitive advantage to other companies that compete against us.

In addition, after a product is approved or cleared for marketing, new data and information, including information about product misuse or abuse at the user level, may lead government agencies, professional societies, practice management groups or patient or trade organizations to recommend or publish guidance or guidelines related to the use of our products, which may lead to reduced sales of our products. For example, in May 2016, an FDA advisory panel recommended mandatory training of all physicians who prescribe opioids on the risks of prescription opioids. In 2016, the U.S. Centers for Disease Control and Prevention also issued a guideline for prescribing opioids for chronic pain that provides recommendations for primary care clinicians prescribing opioids for chronic pain outside of active cancer treatment, palliative care and end-of-life care. In addition, state health departments and boards of pharmacy have authority to regulate distribution and may modify their regulations with respect to prescription opioid medications in an attempt to curb abuse. These or any new regulations or requirements could be difficult and expensive for us to comply with and could have a material adverse effect on our business, financial condition, results of operations and cash flows.

The FDA scheduled a Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee in March 2017 to discuss pre- and post-marketing data about the abuse of OPANA® ER and the overall risk-benefit of this product. The advisory committees were also scheduled to discuss abuse of generic oxymorphone ER and oxymorphone immediate-release products. In March 2017, the advisory committees voted 18 to eight, with one abstention, that the benefits of reformulated OPANA® ER no longer outweigh its risks. While several of the advisory committee members acknowledged the role of OPANA® ER in clinical practice, others believed its benefits were overshadowed by the continuing public health concerns around the product's misuse, abuse and diversion. In June 2017, the FDA requested that we voluntarily withdraw OPANA® ER from the market and, in July 2017, after careful consideration and consultation with the FDA, we decided to voluntarily remove OPANA® ER from the market to the Company's financial detriment. During the second quarter of 2017, we began to work with the FDA to coordinate an orderly withdrawal of the product from the market. By September 1, 2017, we ceased shipments of OPANA® ER to customers and the FDA withdrew the NDA in December 2020. These actions had an adverse effect on our revenues and, as a result of these actions, we incurred certain charges. Actions similar to these, such as recalls or withdrawals, could divert management time and attention, reduce market acceptance of all of our products, harm our reputation, reduce our revenues, lead to additional charges or expenses or result in product liability claims, any of which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Based on scientific developments, post-market experience, legislative or regulatory changes or other factors, the current FDA standards of review for approving new pharmaceutical products, or new indications or uses for approved or cleared products, are sometimes more stringent than those that were applied in the past.

Some new or evolving FDA review standards or conditions for approval or clearance were not applied to many established products currently on the market, including certain opioid products. As a result, the FDA does not have safety databases on these products that are as extensive as some products developed more recently. Accordingly, we believe the FDA may develop such databases for certain of these products, including many opioids. In particular, the FDA has expressed interest in specific chemical structures that may be present as impurities in a number of opioid narcotic APIs, such as oxycodone, which, based on certain structural characteristics and laboratory tests, may indicate the potential for having mutagenic effects. The FDA has required, and may continue to require, more stringent controls of the levels of these or other impurities in products.

Also, the FDA may require labeling revisions, formulation or manufacturing changes and/or product modifications for new or existing products containing impurities. More stringent requirements, together with any additional testing or remedial measures that may be necessary, could result in increased costs for, or delays in, obtaining approvals. Although we do not believe that the FDA would seek to remove a currently marketed product from the market unless the effects of alleged impurities are believed to indicate a significant risk to patient health, we cannot make any such assurance.

The FDA's exercise of its authority under the FFDCA could result in delays or increased costs during product development, clinical trials and regulatory review, increased costs to comply with additional post-approval regulatory requirements and potential restrictions on sales of approved products. For example, in 2015, the FDA sent letters to a number of manufacturers, including Endo, requiring that a randomized, double-blind, placebo-controlled clinical trial be conducted to evaluate the effect of TRT on the incidence of major adverse cardiovascular events in men. The letter received by Endo required that we include new safety information in the labeling and Medication Guide for certain prescription medications containing testosterone, such as TESTIM®.

Post-marketing studies and other emerging data about marketed products, such as adverse event reports, may adversely affect sales of our products. Furthermore, the discovery of significant safety or efficacy concerns or problems with a product in the same therapeutic class as one of our products that implicate or appear to implicate the entire class of products could have an adverse effect on sales of our product or, in some cases, result in product withdrawals. The FDA has continuing authority over the approval of an NDA, ANDA or BLA and may withdraw approval if, among other reasons, post-marketing clinical or other experience, tests or data show that a product is unsafe for use under the conditions upon which it was approved or licensed, or if FDA determines that there is a lack of substantial evidence of the product's efficacy under the conditions described in its labeling.

In addition to the FDA and other U.S. regulatory agencies, non-U.S. regulatory agencies may have authority over various aspects of our business and may impose additional requirements and costs. Similar to other healthcare companies, our facilities in multiple countries across the full range of our business units are subject to routine and new-product related inspections by regulatory authorities including the FDA, the Medicines and Healthcare products Regulatory Agency, the Health Products Regulatory Authority and Health Canada. In the past, some of these inspections have resulted in inspection observations (including FDA Form 483 observations). Future inspections may result in additional inspection observations or other corrective actions, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Certain of our products contain controlled substances. Stringent DEA and other governmental regulations on our use of controlled substances include restrictions on their use in research, manufacture, distribution and storage. A breach of these regulations could result in imposition of civil penalties, refusal to renew or action to revoke necessary registrations, or other restrictions on operations involving controlled substances. In addition, failure to comply with applicable legal requirements could subject the manufacturing facilities of our subsidiaries and manufacturing partners to possible legal or regulatory action, including shutdown. Any such shutdown may adversely affect their ability to manufacture or supply product and thus, our ability to market affected products. This could have a material adverse effect on our business, financial condition, results of operations and cash flows. See also the risk described under the caption "The DEA limits the availability of the active ingredients used in many of our products as well as the production of these products, and, as a result, our procurement and production quotas may not be sufficient to meet commercial demand or complete clinical trials."

In addition, we are subject to the U.S. Drug Supply Chain Security Act (DSCSA), which requires development of an electronic pedigree to track and trace each prescription product at the salable unit level through the distribution system. The DSCSA becomes effective incrementally over a 10-year period from its enactment on November 27, 2013. Compliance with DSCSA and future U.S. federal or state electronic pedigree requirements could require significant capital expenditures, increase our operating costs and impose significant administrative burdens.

We cannot determine what effect changes in laws, regulations or legal interpretations or requirements by the FDA, the courts or others, when and if promulgated or issued, or advisory committee meetings may have on our business in the future. Changes could, among other things, require expanded or different labeling, additional testing, monitoring of patients, interaction with physicians, education programs for patients or physicians, curtailment of necessary supplies, limitations on product distribution, the recall or discontinuance of certain products and additional recordkeeping. Any such changes could result in additional litigation and may have a material adverse effect on our business, financial condition, results of operations and cash flows. The evolving and complex nature of regulatory science and regulatory requirements, the broad authority and discretion of the FDA and the generally high level of regulatory oversight results in a continuing possibility that, from time to time, we will be adversely affected by regulatory actions despite our ongoing efforts and commitment to achieve and maintain full compliance with all regulatory requirements.

Certain of these risks could be exacerbated by the impact of COVID-19.

Our reporting and payment obligations under Medicaid and other governmental drug pricing programs are complex and may involve subjective decisions. Any failure to comply with those obligations could subject us to penalties and sanctions.

We are subject to federal and state laws prohibiting the presentation (or the causing to be presented) of claims for payment (by Medicare, Medicaid or other third-party payers) that are determined to be false or fraudulent, including presenting a claim for an item or service that was not provided. These false claims statutes include the federal civil FCA, which permits private persons to bring suit in the name of the government alleging false or fraudulent claims presented to or paid by the government (or other violations of the statutes) and to share in any amounts paid by the entity to the government in fines or settlement. Such suits, known as *qui tam* actions, have increased significantly in the healthcare industry in recent years. These actions against pharmaceutical companies, which do not require proof of a specific intent to defraud the government, may result in payment of fines to and/or administrative exclusion from the Medicare, Medicaid and/or other government healthcare programs.

We are subject to laws that require us to enter into a Medicaid Drug Rebate Agreement, a 340B Pharmaceutical Pricing Agreement and agreements with the Department of Veterans Affairs as a condition for having our products eligible for payment under Medicare Part B and Medicaid. We have entered into such agreements. In addition, we are required to report certain pricing information to CMS, the Health Resources and Services Administration and the Department of Veterans Affairs on a periodic basis to facilitate rebate payments to the State Medicaid Programs, to set Medicare Part B reimbursement levels and to establish the prices that can be charged to certain purchasers, including 340B-covered entities and certain government entities. Any failure to comply with these laws and agreements could have a material adverse effect on our business, financial condition, results of operations and cash flows.

With regard to Medicaid, on February 1, 2016, CMS issued a Final Rule implementing the Medicaid Drug Rebate provisions incorporated into the PPACA, effective April 1, 2016 in most instances. Ongoing compliance with these program rules, including the requirement that we adopt reasonable assumptions where law, regulation and guidance do not address specific participation issues, may impact the level of rebates that we owe under the program. The 2016 Final Rule also expanded the scope of Medicaid to apply to U.S. territories effective on January 1, 2023), which will require operational adjustments and may result in additional rebate liability. Additionally, in December 2020, CMS issued a Final Rule for Medicaid that makes changes with regard to: (i) the calculation of Medicaid Best Price for certain value- or outcomes-based discounting arrangements; (ii) the standard for excluding the value of manufacturer copayment assistance and other patient support arrangements from the calculation of Average Manufacturer Price and Best Price; (iii) the identification of "line extension" drugs that are subject to higher Medicaid rebate liability; and (iv) establishment of additional drug utilization review requirements for opioids. Depending on how these changes are implemented, they could have a material adverse effect on our business, financial condition, results of operations and cash flows.

We and other pharmaceutical companies have been named as defendants in a number of lawsuits filed by various government entities, alleging generally that we and numerous other pharmaceutical companies reported false pricing information in connection with certain products that are reimbursable by state Medicaid programs, which are partially funded by the federal government. There is a risk we will be subject to similar investigations or litigations in the future, that we will suffer adverse decisions or verdicts of substantial amounts or that we will enter into monetary settlements. Any unfavorable outcomes as a result of such proceedings could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Decreases in the degree to which individuals are covered by healthcare insurance could result in decreased use of our products.

Employers may seek to reduce costs by reducing or eliminating employer group healthcare plans or transferring a greater portion of healthcare costs to their employees. Job losses or other economic hardships, including any that may be related to COVID-19, may also result in reduced levels of coverage for some individuals, potentially resulting in lower levels of healthcare coverage for themselves or their families. Further, in addition to the fact that the TCJA eliminated the PPACA's requirement that individuals maintain insurance or face a penalty, additional steps to limit or end cost-sharing subsidies to lower-income Americans may increase instability in the insurance marketplace and the number of uninsured Americans. These economic conditions may affect patients' ability to afford healthcare as a result of increased co-pay or deductible obligations, greater cost sensitivity to existing co-pay or deductible obligations and lost healthcare insurance coverage or for other reasons. We believe such conditions could lead to changes in patient behavior and spending patterns that negatively affect usage of certain of our products, including some patients delaying treatment, rationing prescription medications, leaving prescriptions unfilled, reducing the frequency of visits to healthcare facilities, utilizing alternative therapies or foregoing healthcare insurance coverage. Such changes may result in reduced demand for our products, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

If our manufacturing facilities are unable to manufacture our products or we face interruptions in the manufacturing process due to regulatory or other factors, it could have a material adverse effect on our business, financial condition, results of operations and cash flows.

If any of our or our third-party manufacturing facilities fail to comply with regulatory requirements or encounter other manufacturing difficulties, it could adversely affect our ability to supply products. All facilities and manufacturing processes used for the manufacture of pharmaceutical products are subject to inspection by regulatory agencies at any time and must be operated in conformity with cGMP and, in the case of controlled substances, DEA regulations. Compliance with the FDA's cGMP and DEA requirements applies to both products for which regulatory approval is being sought and to approved products. In complying with cGMP requirements, pharmaceutical manufacturing facilities must continually expend significant time, money and effort in production, recordkeeping, quality assurance and quality control so that their products meet applicable specifications and other requirements for product safety, efficacy and quality. Failure to comply with applicable legal requirements subjects our or our third-party manufacturing facilities to possible legal or regulatory action, including shutdown, which may adversely affect our ability to supply our products. Additionally, our facilities and our third-party manufacturing facilities may face other significant disruptions due to labor strikes, failure to reach acceptable agreement with labor unions, infringement of intellectual property rights, vandalism, natural disaster, outbreak and spread of viral or other diseases, storm or other environmental damage, civil or political unrest, export or import restrictions or other events. If we are not able to manufacture products at our or our third-party manufacturing facilities because of regulatory, business or any other reasons, the manufacture and marketing of these products could be interrupted. This could have a material adverse effect on our business, financial condition, results of operations and cash flows.

For example, the manufacturing facilities qualified to manufacture the enzyme CCH, which is included in XIAFLEX®, are subject to such regulatory requirements and oversight. If such facilities fail to comply with cGMP requirements, we may not be permitted to sell our products or may be limited in the jurisdictions in which we are permitted to sell them. Further, if an inspection by regulatory authorities indicates that there are deficiencies, including non-compliance with regulatory requirements, we could be required to take remedial actions, stop production or close our facilities, which could disrupt the manufacturing processes and could limit the supply of CCH and/or delay clinical trials and subsequent licensure and/or limit the sale of commercial supplies. In addition, future noncompliance with any applicable regulatory requirements may result in refusal by regulatory authorities to allow use of CCH in clinical trials, refusal by the government to allow distribution of CCH within the U.S. or other jurisdictions, criminal prosecution, fines, recall or seizure of products, total or partial suspension of production, prohibitions or limitations on the commercial sale of products, refusal to allow the entering into of federal and state supply contracts and civil litigation.

We purchase certain API and other materials used in our manufacturing operations from foreign and U.S. suppliers. The price and availability of API and other materials is subject to volatility for a number of reasons, many of which may be outside of our control. There is no guarantee that we will always have timely, sufficient or affordable access to critical raw materials or supplies from third parties. An increase in the price, or an interruption in the supply, of any API or raw material could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Non-U.S. regulatory requirements vary, including with respect to the regulatory approval process, and failure to obtain regulatory approval or maintain compliance with requirements in non-U.S. jurisdictions would prevent or impact the marketing of our products in those jurisdictions.

We have worldwide intellectual property rights to market many of our products and product candidates and may seek approval to market certain of our existing or potential future products outside of the U.S. Approval of a product by the regulatory authorities of a particular country is generally required prior to manufacturing or marketing that product in that country. The approval procedure varies among countries and can involve additional testing and the time required to obtain such approval may differ from that required to obtain FDA approval. Non-U.S. regulatory approval processes generally include risks similar to those associated with obtaining FDA approval, as further described herein. FDA approval does not guarantee approval by the regulatory authorities of any other country, nor does the approval by foreign regulatory authorities in one country guarantee approval by regulatory authorities in other foreign countries or by the FDA.

Outside of the U.S., regulatory agencies generally evaluate and monitor the safety, efficacy and quality of pharmaceutical products and devices and impose regulatory requirements applicable to manufacturing processes, stability testing, recordkeeping and quality standards, among others. These requirements vary by jurisdiction. In certain countries, the applicable healthcare and drug regulatory regimes may continue to evolve and implement new requirements. Ensuring and maintaining compliance with these varying and evolving requirements is and will continue to be difficult, time-consuming and costly. In seeking regulatory approvals in non-U.S. jurisdictions, we must also continue to comply with U.S. laws and regulations, including those imposed by the FCPA. See the risk factor "The risks related to our global operations may adversely impact our revenues, results of operations and financial condition." If we fail to comply with these various regulatory requirements or fail to obtain and maintain required approvals, our target market will be reduced and our ability to generate non-U.S. revenue will be adversely affected.

If pharmaceutical companies are successful in limiting the use of generics through their legislative, regulatory and other efforts, our sales of generic products may suffer.

Many pharmaceutical companies increasingly have used state and federal legislative and regulatory means to delay generic competition. These efforts have included:

- pursuing new patents for existing products which may be granted just before the expiration of earlier patents, which could extend patent protection for additional years;
- using the Citizen Petition process (for example, under 21 C.F.R. § 10.30) to request amendments to FDA standards;
- attempting to use the legislative and regulatory process to have products reclassified or rescheduled or to set definitions of abuse-deterrent formulations to protect patents and profits; and
- engaging in state-by-state initiatives to enact legislation that restricts the substitution of some generic products.

If pharmaceutical companies or other third parties are successful in limiting the use of generic products through these or other means, our sales of generic products and our growth prospects may decline, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

New tariffs and evolving trade policy between the U.S. and other countries, including China, could have a material adverse effect on our business, financial condition, results of operations and cash flows.

We conduct business globally and our operations, including third-party suppliers, span numerous countries outside the U.S. There is uncertainty about the future relationship between the U.S. and various other countries with respect to trade policies, treaties, government regulations and tariffs.

The U.S. government may seek to impose additional restrictions on international trade, such as increased tariffs on goods imported into the U.S. Such tariffs could potentially disrupt our existing supply chains and impose additional costs on our business, including costs with respect to raw materials upon which our business depends. Furthermore, if tariffs, trade restrictions or trade barriers are placed on products such as ours by foreign governments, it could cause us to raise prices for our products, which may result in the loss of customers. If we are unable to pass along increased costs to our customers, our margins could be adversely affected. Additionally, it is possible that further tariffs may be imposed that could affect imports of APIs and other materials used in our products, or our business may be adversely impacted by retaliatory trade measures taken by other countries, including restricted access to APIs or other materials used in our products, causing us to raise prices or make changes to our products. Further, the continued threats of tariffs, trade restrictions and trade barriers could have a generally disruptive impact on the global economy and, therefore, negatively impact our sales. Given the volatility and uncertainty regarding the scope and duration of these tariffs and other aspects of U.S. international trade policy, the impact on our operations and results is uncertain and could be significant. Further governmental action related to tariffs, additional taxes, regulatory changes or other retaliatory trade measures could occur in the future. Any of these factors could have a material adverse effect on our business, financial condition, results of operations and cash flows.

We are subject to information privacy and data protection laws that include penalties for noncompliance. Our failure to comply with various laws protecting the confidentiality of personal information, patient health information or other data could result in penalties and reputational damage.

We are subject to a number of privacy and data protection laws and regulations globally. The legislative and regulatory landscape for privacy and data security continues to evolve. Certain countries in which we operate have, or are developing, laws protecting the confidentiality of individually identifiable personal information, including patient health information. This includes federal and state laws and regulations in the U.S. as well as in Europe and other markets.

For example, multiple U.S. states have passed data privacy legislation that provides new data privacy rights for consumers and new operational requirements for businesses. The California Consumer Privacy Act of 2018 (CCPA) went into effect on January 1, 2020 and established a new privacy framework for covered businesses by creating an expanded definition of personal information, establishing new data privacy rights for consumers in the state of California and creating a new and potentially severe statutory damages framework for violations of the CCPA and for businesses that fail to implement reasonable security procedures and practices to prevent data breaches. In 2021, Virginia and Colorado passed laws similar in scope to the CCPA and California voters passed an update to the CCPA, the California Privacy Rights Act, which expanded on the existing consumer rights under the CCPA, imposed additional obligations on governed businesses and created a new state enforcement agency dedicated to enforcing California consumers' privacy rights. State legislatures can be expected to continue to regulate data privacy in the absence of legislation from the U.S. federal government. Many aspects of the CCPA and new state privacy laws have not been interpreted by courts and best practices are still being developed, all of which increase the risk of compliance failure and related adverse impacts.

In addition, data protection laws in other international jurisdictions impose restrictions on our authority to collect, analyze and transfer personal data, including health data, across international borders. For example, the EU's General Data Protection Regulation (GDPR), which became enforceable as of May 25, 2018, and related implementing laws in individual EU Member States strictly regulate our ability to collect, analyze and transfer personal data regarding persons in the EU, including health data from clinical trials and adverse event reporting. The GDPR, which has extra-territorial scope and substantial fines for breaches (up to 4% of global annual revenue or €20 million, whichever is greater) grants individuals whose personal data (which is very broadly defined) is collected or otherwise processed the right to access the data, request its deletion and control its use and disclosure. The GDPR also requires notification of a breach in the security of such data to be provided within 72 hours of discovering the breach. Although the GDPR itself is self-executing across all EU Member States, data protection authorities from different EU Member States may interpret and apply the regulation somewhat differently, which adds to the complexity of processing personal data in the EU. Uncertainty in the interpretation and enforcement of the regulation by the EU Member States' different data protection authorities contributes to liability exposure risk.

The GDPR prohibits the transfer of personal data to countries outside of the EU that are not considered by the European Commission to provide an adequate level of data protection, and transfers of personal data to such countries may be made only in certain circumstances, such as where the transfer is necessary for important reasons of public interest or the individual to whom the personal data relates has given his or her explicit consent to the transfer after being informed of the risks involved. Even when certain circumstances are met, a July 2020 decision by the Court of Justice of the European Union (Schrems II), placed transfers of personal data from the EU to the U.S. under considerable uncertainty as the decision raised concerns about governmental entity access to personal data under U.S. national security laws. Transfers of personal data out of the EU to the U.S. remain an unresolved matter for political negotiation between the U.S. and EU representatives.

Similar international data privacy laws also impose stringent requirements on the collection, use of and ability to analyze and transfer personal data from each country and increase the complexity of our global operations. In all cases, enforcement of international data privacy laws and regulations is new, or priorities are shifting, which may constrain the implementation of global business processes and may impose additional costs for compliance.

We have policies and practices that we believe make us compliant with applicable privacy regulations. Nevertheless, there remains a risk of failure to comply with the rules arising from the GDPR or privacy laws in other jurisdictions in which we operate. Should a transgression be deemed to have occurred, it could lead to government enforcement actions and significant sanctions or penalties against us, adversely impact our results of operations and subject us to negative publicity. Such liabilities could materially affect our operations.

There has also been increased enforcement activity in the U.S. particularly related to data security breaches. A violation of these laws or regulations by us or our third-party vendors could subject us to penalties, fines, liability and/or possible exclusion from Medicare or Medicaid. Such sanctions could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Intellectual Property Related Risks

Our ability to protect and maintain our proprietary and licensed third-party technology, which is vital to our business, is uncertain.

Our success, competitive position and future income depend in part on our ability, and the ability of our partners and suppliers, to obtain and protect patent and other intellectual property rights relating to our current and future technologies, processes and products. The degree of protection any patents will afford is uncertain, including whether the protection obtained will be of sufficient breadth and degree to protect our commercial interests in all the jurisdictions where we conduct business. That is, the issuance of a patent is not conclusive as to its claimed scope, validity or enforceability. Patent rights may be challenged, revoked, invalidated, infringed or circumvented by third parties. For example, if an invention qualifies as a joint invention, the joint inventor may have intellectual property rights in the invention, which might not be protected. A third party may also infringe upon, design around or develop uses not covered by any patent issued or licensed to us and our patents may not otherwise be commercially viable. In this regard, the patent position of pharmaceutical compounds and compositions is particularly uncertain and involves complex legal and factual questions. Even issued patents may later be modified or revoked by the PTO, by comparable foreign patent offices or by a court following legal proceedings. Laws relating to such rights may in the future also be changed or withdrawn.

There is no assurance that any of our patent claims in our pending non-provisional and provisional patent applications relating to our technologies, processes or products will be issued or, if issued, that any of our existing and future patent claims will be held valid and enforceable against third-party infringement. We could incur significant costs and management distraction if we initiate litigation against others to protect or enforce our intellectual property rights. Such patent disputes may be lengthy and a potential violator of our patents may bring a potentially infringing product to market during the dispute, subjecting us to competition and damages due to infringement of the competitor product. Upon the expiration or loss of intellectual property protection for a product, others may manufacture and distribute such patented product, which may result in the loss of a significant portion of our sales of that product.

We also rely on trade secrets and other unpatented proprietary information, which we generally seek to protect by confidentiality and nondisclosure agreements with our employees, consultants, advisors and partners. These agreements may not effectively prevent disclosure of confidential information and may not provide us with an adequate remedy in the event of unauthorized disclosure. Even if third parties misappropriate or infringe upon our proprietary rights, we may not be able to discover or determine the extent of any such unauthorized use and we may not be able to prevent third parties from misappropriating or infringing upon our proprietary rights. In addition, if our employees, scientific consultants or partners develop inventions or processes that may be applicable to our existing products or products under development, such inventions and processes will not necessarily become our property and may remain the property of those persons or their employers.

Any failure by us to adequately protect our technology, trade secrets or proprietary know-how or to enforce our intellectual property rights could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Our competitors or other third parties may allege that we are infringing their intellectual property, forcing us to expend substantial resources in litigation, the outcome of which is uncertain. Any unfavorable outcome of such litigation, including losses related to "at-risk" product launches, could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Companies that produce branded pharmaceutical products routinely bring litigation against ANDA or similar applicants that seek regulatory approval to manufacture and market generic forms of branded products, alleging patent infringement or other violations of intellectual property rights. Patent holders may also bring patent infringement suits against companies that are currently marketing and selling approved generic products. Litigation often involves significant expense. Additionally, if the patents of others are held valid, enforceable and infringed by our current products or future product candidates, we would, unless we could obtain a license from the patent holder, need to delay selling our corresponding generic product and, if we are already selling our product, cease selling and potentially destroy existing product stock. Additionally, we could be required to pay monetary damages or royalties to license proprietary rights from third parties and we may not be able to obtain such licenses on commercially reasonable terms or at all.

There may be situations in which we may make business and legal judgments to market and sell products that are subject to claims of alleged patent infringement prior to final resolution of those claims by the courts based upon our belief that such patents are invalid, unenforceable or are not infringed by our marketing and sale of such products. This is commonly referred to in the pharmaceutical industry as an "at-risk" launch. The risk involved in an at-risk launch can be substantial because, if a patent holder ultimately prevails against us, the remedies available to such holder may include, among other things, damages calculated based on the profits lost by the patent holder, which can be significantly higher than the profits we make from selling the generic version of the product. Moreover, if a court determines that such infringement is willful, the damages could be subject to trebling. We could face substantial damages from adverse court decisions in such matters. We could also be at risk for the value of such inventory that we are unable to market or sell.

Tax Related Risks

Future changes to tax laws could materially adversely affect us.

Under current law, we expect Endo International plc to be treated as a non-U.S. corporation for U.S. federal income tax purposes. However, changes to the rules in Section 7874 of the Internal Revenue Code (the Code) or regulations promulgated thereunder or other guidance issued by the Treasury or the IRS could adversely affect our status as a non-U.S. corporation for U.S. federal income tax purposes, and any such changes could have prospective or retroactive application to us, EHSI and/or their respective shareholders and affiliates. Consequently, there can be no assurance that there will not exist in the future a change in law that might cause us to be treated as a U.S. corporation for U.S. federal income tax purposes, including with retroactive effect. Further, we are continuing to evaluate the Inflation Reduction Act of 2022 and its requirements, as well as any potential impact on our business. Based on our current analysis of the act, we do not believe this legislation will have a material impact on our provision for income taxes.

In addition, Ireland's Department of Finance, Luxembourg's Ministry of Finance, the Organization for Economic Co-operation and Development, the European Commission and other government agencies in jurisdictions where we and our affiliates do business, including the U.S. Congress, have had an extended focus on issues related to the taxation of multinational corporations. There are several proposals pending in various jurisdictions in which we do business that, if enacted, would substantially change the taxation of multinational corporations. As a result, the tax laws in the jurisdictions in which we operate could change on a prospective or retroactive basis, and any such changes could affect recorded deferred tax assets and liabilities and increase our effective tax rate, which could have a material adverse effect on our business, financial condition, results of operations and cash flows. The potential impact of changes in tax laws in such jurisdictions could have a material impact on the Company.

The IRS may not agree with the conclusion that we should be treated as a non-U.S. corporation for U.S. federal income tax purposes.

Although Endo International plc is incorporated in Ireland, the IRS may assert that it should be treated as a U.S. corporation (and, therefore, a U.S. tax resident) for U.S. federal income tax purposes pursuant to Section 7874 of the Code. A corporation is generally considered a tax resident in the jurisdiction of its organization or incorporation for U.S. federal income tax purposes. Because we are an Irish incorporated entity, we would generally be classified as a non-U.S. corporation (and, therefore, a non-U.S. tax resident) under these rules. Section 7874 provides an exception pursuant to which a non-U.S. incorporated entity may, in certain circumstances, be treated as a U.S. corporation for U.S. federal income tax purposes.

Under Section 7874, we would be treated as a non-U.S. corporation for U.S. federal income tax purposes if the former shareholders of EHSI owned, immediately after the Paladin transactions (within the meaning of Section 7874), less than 80% (by both vote and value) of Endo shares by reason of holding shares in EHSI (the ownership test). The former EHSI shareholders owned less than 80% (by both vote and value) of the shares in Endo after the Paladin merger by reason of their ownership of shares in EHSI. As a result, under current law, we expect Endo International plc to be treated as a non-U.S. corporation for U.S. federal income tax purposes. There is limited guidance regarding the application of Section 7874, including with respect to the provisions regarding the application of the ownership test. Our obligation to complete the Paladin transactions was conditional upon receipt of a Section 7874 opinion from our counsel, Skadden, Arps, Slate, Meagher & Flom LLP (Skadden), dated as of the closing date of the Paladin transactions and subject to certain qualifications and limitations set forth therein, to the effect that Section 7874 and the regulations promulgated thereunder should not apply in such a manner so as to cause Endo to be treated as a U.S. corporation for U.S. federal income tax purposes from and after the closing date. However, an opinion of tax counsel is not binding on the IRS or a court. Therefore, there can be no assurance that the IRS will not take a position contrary to Skadden's Section 7874 opinion or that a court will not agree with the IRS in the event of litigation.

The effective rate of taxation upon our results of operations is dependent on multi-national tax considerations.

Our effective income tax rate in the future could be adversely affected by a number of factors, including changes in the geographic mix of pre-tax earnings among jurisdictions with differing statutory tax rates, changes in the valuation of deferred tax assets and liabilities, changes in tax laws, the outcome of income tax audits and the repatriation of earnings from our subsidiaries for which we have not provided for taxes. Cash repatriations are subject to restrictions in certain jurisdictions and may be subject to withholding and other taxes. We periodically assess our tax positions to determine the adequacy of our tax provisions, which are subject to significant discretion. Although we believe our tax provisions are adequate, the final determination of tax audits and any related disputes could be materially different from our historical income tax provisions and accruals. The results of audits and disputes could have a material adverse effect on our business, financial condition, results of operations and cash flows for the period or periods for which the applicable final determinations are made.

The IRS and other taxing authorities may continue to challenge our tax positions and we may not be able to successfully maintain such positions.

We are incorporated in Ireland and also maintain subsidiaries in, among other jurisdictions, the U.S., Canada, India, the United Kingdom and Luxembourg. The IRS and other taxing authorities may continue to challenge our tax positions. The IRS presently is examining certain of our subsidiaries' U.S. income tax returns for fiscal years ended between December 31, 2011 and December 31,

2015 and, in connection with those examinations, is reviewing our tax positions related to, among other things, certain intercompany arrangements, including the level of profit earned by our U.S. subsidiaries pursuant to such arrangements, and a product liability loss carryback claim.

During the third quarter of 2020, the IRS opened an examination into certain of our subsidiaries' U.S. income tax returns for fiscal years ended between December 31, 2016 and December 31, 2018. The IRS will likely examine our tax returns for other fiscal years and/or for other tax positions. Similarly, other tax authorities are currently examining our non-U.S. tax returns. Additionally, other jurisdictions where we are not currently under audit remain subject to potential future examinations. Such examinations may lead to proposed or actual adjustments to our taxes that may be material, individually or in the aggregate.

For additional information, including a discussion of related recent developments and their potential impact on us, refer to Note 21. Income Taxes in the Consolidated Financial Statements included in Part IV, Item 15 of this report.

Responding to or defending any challenge or proposed adjustment to our tax positions is expensive, consumes time and other resources and diverts management's attention. We cannot predict whether taxing authorities will conduct an audit challenging any of our tax positions, the cost involved in responding to and defending any such audit and resulting litigation, or the outcome. If we are unsuccessful in any of these matters, we may be required to pay taxes for prior periods, interest, fines or penalties, and may be obligated to pay increased taxes in the future or repay certain tax refunds, any of which could require us to reduce our operating costs, decrease efforts in support of our products or seek to raise additional funds, all of which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Our ability to use tax attributes to offset U.S. taxable income may be limited.

Existing and future tax laws and regulations may limit our ability to use U.S. tax attributes including, but not limited to, net operating losses (NOLs) and excess interest expense, to offset U.S. taxable income. For a period of time following the 2014 Paladin transactions, Section 7874 of the Code precludes our U.S. affiliates from utilizing U.S. tax attributes to offset taxable income if we complete certain transactions with related non-U.S. subsidiaries.

In addition, our tax attributes and future tax deductions may be reduced or significantly limited as a result of our voluntary petitions for relief under the Bankruptcy Code. Generally, any discharge of our external or internal debt obligations as a result of our chapter 11 filing for an amount less than the adjusted issue price may give rise to cancellation of indebtedness income, which must either be included in our taxable income or result in a reduction to our tax attributes. Certain tax attributes otherwise available and of value to the Company may be reduced, in most cases by the principal amount of the indebtedness forgiven. U.S. and non U.S. tax attributes subject to reduction include: (i) NOLs and NOL carryforwards; (ii) credit carryforwards; (iii) capital losses and capital loss carryforwards; and (iv) the tax basis of the Company's depreciable, amortizable and other assets.

To the extent, if any, that U.S. NOL carryforwards, other losses and credits generated by us during or prior to our bankruptcy proceedings are available as deductions following our bankruptcy proceedings, our ability to utilize such deductions may be limited by Section 382 of the Code. Section 382 provides rules limiting the utilization of a corporation's NOLs and other losses, deductions and credits following a more than 50% change in ownership of a corporation's equity (an "ownership change"). An ownership change may occur with respect to the Company in connection with bankruptcy, unless the Section 382(l)(5) exception applies. This exception is not easily met as it requires a majority of the holders of the Company's stock after bankruptcy to meet certain specific and narrow conditions. Therefore, the Company's U.S. NOLs may be significantly limited by Section 382 of the Code. The amount of the Company's post-ownership-change annual U.S. taxable income that can be offset by the pre-ownership-change U.S. NOLs generally cannot exceed an amount equal to the product of: (i) the applicable federal long-term tax exempt rate in effect on the date of the ownership change and (ii) the value of the Company's U.S. affiliate stock (the Annual Limitation). However, if the value of the Company's U.S. affiliate stock is zero, if the Company does not continue its historic business or use a significant portion of its assets in a new business for two years after the ownership change, the Annual Limitation resulting from the ownership change is zero and the Company may be significantly limited in its ability to use any of its U.S. NOLs that originated during or prior to its bankruptcy proceedings. In addition, if the Company has a net unrealized built-in loss at the time of an ownership change, future deductions for items such as amortization, depreciation and settlement liabilities may also be significantly limited.

Further, if we or any of our affiliates undertake sales of any of our assets in connection with the bankruptcy, such sales may result in: (i) a reduction in our available tax attributes; (ii) an inability for us to proactively use our tax attributes; and (iii) us incurring a material amount of tax.

Any loss of or limitations on our ability to use any of the tax attributes described above or any other tax attributes could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Structural and Organizational Risks

We are incorporated in Ireland and Irish law differs from the laws in effect in the U.S. and may afford less protection to, or otherwise adversely affect, our shareholders.

Our shareholders may have more difficulty protecting their interests than would shareholders of a corporation incorporated in a jurisdiction of the U.S. As an Irish company, we are governed by Irish Companies Act 2014 (the Companies Act). The Companies Act and other relevant aspects of Irish law differ in some material respects from laws generally applicable to U.S. corporations and shareholders, including, among others, the provisions relating to interested director and officer transactions, acquisitions, takeovers, shareholder lawsuits and indemnification of directors. For example, under Irish law, the duties of directors and officers of a company are generally owed to the company only. As a result, shareholders of Irish companies generally do not have a personal right of action against the directors or officers of a company and may pursue a right of action on behalf of the company only in limited circumstances. In addition, depending on the circumstances, the acquisition, ownership and/or disposition of our ordinary shares may subject individuals to different or additional tax consequences under Irish law including, but not limited to, Irish stamp duty, dividend withholding tax and capital acquisitions tax.

Any attempts to take us over will be subject to Irish Takeover Rules and subject to review by the Irish Takeover Panel.

We are subject to Irish Takeover Rules, under which the Board will not be permitted to take any action which might frustrate an offer for our ordinary shares once it has received an approach which may lead to an offer or has reason to believe an offer is imminent.

We are an Irish company and it may be difficult to enforce judgments against us or certain of our officers and directors.

We are incorporated in Ireland and a substantial portion of our assets are located in jurisdictions outside the U.S. In addition, some of our officers and directors reside outside the U.S., and some or all of their respective assets are or may be located in jurisdictions outside of the U.S. It may be difficult for investors to effect service of process against us or such officers or directors or to enforce, against us or them, judgments of U.S. courts predicated upon civil liability provisions of the U.S. federal securities laws.

There is no treaty between Ireland and the U.S. providing for the reciprocal enforcement of foreign judgments. The following requirements must be met before a foreign judgment will be deemed to be enforceable in Ireland:

- the judgment must be for a definite sum;
- the judgment must be final and conclusive; and
- the judgment must be provided by a court of competent jurisdiction.

An Irish court will also exercise its right to refuse judgment if the foreign judgment was obtained by fraud, if the judgment violated Irish public policy, if the judgment is in breach of natural justice or if it is irreconcilable with an earlier judgment. Further, an Irish court may stay proceedings if concurrent proceedings are being brought elsewhere. Judgments of U.S. courts of liabilities predicated upon U.S. federal securities laws may not be enforced by Irish courts if deemed to be contrary to public policy in Ireland.

Item 1B. ***Unresolved Staff Comments***

None.

Item 2. ***Properties***

This section provides information about the location and general character of the Company's principal physical properties at December 31, 2022.

The Company's global headquarters is located in Dublin, Ireland. The Company also conducts certain corporate functions at its Malvern, Pennsylvania location. Both properties are leased. The Malvern lease is described in more detail in Note 9. Leases in the Consolidated Financial Statements included in Part IV, Item 15 of this report. These locations support each of our reportable segments. For example, our global quality, supply chain and clinical development functions are run from our global headquarters. The Company's segments conduct certain additional business functions, including manufacturing, distribution, quality assurance, R&D and administration, at locations throughout the U.S. and select global markets. Additional information about the properties of the Company's reportable segments is set forth below:

- Branded Pharmaceuticals: This segment also conducts certain operations in the U.S. through leased and owned manufacturing properties in Pennsylvania, New Jersey and Michigan, as well as certain administrative and R&D functions through leased properties in Pennsylvania.
- Sterile Injectables: This segment also conducts certain manufacturing, quality assurance, R&D and administrative functions in the U.S. through owned and leased properties in Michigan, as well as certain R&D and administrative functions in New Jersey and India in the same facilities as our Generic Pharmaceuticals segment, as discussed below.
- Generic Pharmaceuticals: This segment also conducts certain administrative functions through a leased property in New Jersey, as well as significant R&D operations and manufacturing and administrative functions in India through owned and leased facilities in Chennai, Indore and Mumbai.
- International Pharmaceuticals: This segment's operations are currently conducted through Paladin's leased headquarters in Montreal, Canada.

As of December 31, 2022, our owned and leased properties consist of approximately 1.0 million and 1.1 million square feet, respectively. We believe our properties are suitable and adequate to support our current and projected operations in all material respects.

Item 3. ***Legal Proceedings***

The disclosures under Note 16. Commitments and Contingencies in the Consolidated Financial Statements included in Part IV, Item 15 of this report are incorporated into this Part I, Item 3 by reference.

Item 4. ***Mine Safety Disclosures***

Not applicable.

PART II

Item 5. *Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities*

Market Information. On August 17, 2022, we received a letter (the Notice) from The Nasdaq Stock Market LLC (Nasdaq) stating that, in accordance with Nasdaq Listing Rules 5101, 5110(b) and IM-5101-1, Nasdaq had determined that Endo's ordinary shares would be delisted. In accordance with the Notice, trading of Endo's ordinary shares was suspended at the opening of business on August 26, 2022. As a result, Endo's ordinary shares began trading exclusively on the over-the-counter market on August 26, 2022. On the over-the-counter market, Endo's ordinary shares, which previously traded on the Nasdaq Global Select Market under the symbol ENDP, began to trade under the symbol ENDPQ. On September 14, 2022, Nasdaq filed a Form 25-NSE with the SEC and Endo's ordinary shares were subsequently delisted from the Nasdaq Global Select Market. On December 13, 2022, Endo's ordinary shares were deregistered under Section 12(b) of the Exchange Act.

Over-the-counter market quotations reflect inter-dealer prices, without retail mark-up, mark-down or commission and may not necessarily represent actual transactions.

Holders. As of February 27, 2023, we estimate that there were approximately 190 holders of record of our ordinary shares.

Dividends. We have never declared or paid any cash dividends on our ordinary shares and we currently have no plans to declare a dividend. We are permitted to pay dividends subject to limitations imposed by Irish law, the Bankruptcy Code and related rules during the pendency of the Chapter 11 Cases, the various agreements and indentures governing our indebtedness and the existence of sufficient distributable reserves. For example, the Companies Act requires Irish companies to have distributable reserves equal to or greater than the amount of any proposed dividend. Unless we are able to generate sufficient distributable reserves or create distributable reserves by reducing our share premium account, we will not be able to pay dividends.

Recent sales of unregistered securities; Use of proceeds from registered securities. There were no unregistered sales of equity securities by the Company during the three years ended December 31, 2022.

Purchase of Equity Securities by the issuer and affiliated purchasers. The following table reflects purchases of Endo International plc ordinary shares by the Company during the three months ended December 31, 2022:

Period	Total Number of Shares Purchased	Average Price Paid per Share	Total Number of Shares Purchased as Part of Publicly Announced Plan	Approximate Dollar Value of Shares that May Yet be Purchased Under the Plan (1)
October 1, 2022 to October 31, 2022	—	—	—	$ 2,250,000,000
November 1, 2022 to November 30, 2022	—	—	—	$ 2,250,000,000
December 1, 2022 to December 31, 2022	—	—	—	$ 2,250,000,000
Three months ended December 31, 2022	—	—	—	

(1) Pursuant to Article 11 of the Company's Articles of Association, the Company has broad shareholder authority to conduct ordinary share repurchases by way of redemptions As permitted by Irish Law and the Company's Articles of Association, any ordinary shares redeemed shall be cancelled upon redemption Although the Board has approved the 2015 Share Buyback Program that authorizes the Company to redeem, in the aggregate, $2 5 billion of its outstanding ordinary shares, of which there is approximately $2 3 billion available as of December 31, 2022, we currently do not intend to conduct ordinary share repurchases in the foreseeable future and our ability to do so is restricted during the pendency of the Chapter 11 Cases Redemptions under this program may be made from time to time in open market or negotiated transactions or otherwise, as determined by the Board This program does not obligate the Company to redeem any particular amount of ordinary shares and any repurchase of our ordinary shares under the 2015 Share Buyback Program will be at the sole discretion of the Board and will depend on many factors, including our financial condition, earnings, capital requirements, level of indebtedness, statutory and contractual restrictions applying to the payment of both cash and property dividends or share repurchases (including restrictions imposed by the Bankruptcy Code and related rules and guidelines during the pendency of the Chapter 11 Cases) and other considerations that the Board deems relevant For example, the Companies Act requires Irish companies to have distributable reserves equal to or greater than the amount of any proposed ordinary share repurchase amount In addition, our existing debt instruments restrict or prevent us from paying dividends on our ordinary shares and conducting ordinary share repurchases Agreements governing any future indebtedness, in addition to those governing our current indebtedness, may not permit us to pay dividends on our ordinary shares or conduct ordinary share repurchases Unless we are able to generate sufficient distributable reserves or create distributable reserves by reducing our share premium account, we will not be able to repurchase our ordinary shares To date, the Company has redeemed and cancelled approximately 4 4 million of its ordinary shares under the 2015 Share Buyback Program for $250 0 million, not including related fees The 2015 Share Buyback Program may be suspended, modified or discontinued at any time

Item 6. *Reserved*

Item 7. *Management's Discussion and Analysis of Financial Condition and Results of Operations*

The following Management's Discussion and Analysis of Financial Condition and Results of Operations describes the principal factors affecting the results of operations, liquidity and capital resources and critical accounting estimates of Endo International plc.

This section omits discussions about 2020 items and comparisons between 2021 and 2020. Such discussions can be found in Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations in our Annual Report on Form 10-K for the year ended December 31, 2021.

The discussions in this Management's Discussion and Analysis of Financial Condition and Results of Operations should be read in conjunction with our audited Consolidated Financial Statements and the related Notes thereto. Except for the historical information contained in this report, including the following discussion, this report contains forward-looking statements that involve risks and uncertainties. See "Forward-Looking Statements" beginning on page i of this report.

Unless otherwise indicated or required by the context, references throughout to "Endo," the "Company," "we," "our" or "us" refer to Endo International plc and its subsidiaries.

The operating results of the Company's Astora business are reported as Discontinued operations, net of tax in the Consolidated Statements of Operations for all periods presented. For additional information, see Note 4. Discontinued Operations and Asset Sales in the Consolidated Financial Statements included in Part IV, Item 15 of this report.

EXECUTIVE SUMMARY

This executive summary provides 2022 highlights from the results of operations that follow:

- Total revenues in 2022 were $2,318.9 million compared to $2,993.2 million in 2021 as revenue decreases related to VASOSTRICT® and certain other products in our Sterile Injectables segment, as well as our Branded Pharmaceuticals and International Pharmaceuticals segments, were partially offset by increased revenues from our Generic Pharmaceuticals segment.
- Gross margin percentage in 2022 decreased to 52.9% from 59.2% in 2021, reflecting unfavorable changes in product mix resulting primarily from decreased VASOSTRICT® revenues.
- Asset impairment charges in 2022 increased to $2,142.7 million from $415.0 million in 2021.
- We reported Loss from continuing operations of $2,909.6 million in 2022 compared to Loss from continuing operations of $569.1 million in 2021.

Additionally, the following summary highlights certain recent developments that have resulted in and/or could in the future result in fluctuations in our results of operations and/or changes in our liquidity and capital resources:

- Since 2019, developments related to COVID-19 have continued to evolve rapidly and are likely to continue to do so. The duration and severity of the direct and indirect effects of COVID-19 on our results remain difficult to anticipate and, in many instances, outside of our control. As such, the impacts from COVID-19 on our consolidated results and the results of our business segments to date may not be directly comparable to any historical period and are not necessarily indicative of its impact on our results for any future periods, and the evolving nature of the COVID-19 pandemic could increase the degree to which our results, including the results of our business segments, fluctuate in the future. Additionally, the numerous uncertainties related to COVID-19 have impacted our ability to forecast our future operations; however, any future impact could be material.
- In November 2020, we announced the initiation of several strategic actions, collectively referred to herein as the 2020 Restructuring Initiative, to further optimize operations and increase overall efficiency. We recorded certain charges to complete these actions in anticipation of realizing annualized cost savings. For further discussion of these actions, including a discussion of amounts recognized, refer to Note 5. Restructuring in the Consolidated Financial Statements included in Part IV, Item 15 of this report.
- In March 2021, we completed a series of financing transactions, collectively referred to herein as the March 2021 Refinancing Transactions, which are further discussed in Note 15. Debt in the Consolidated Financial Statements included in Part IV, Item 15 of this report.
- In November 2021, our PSP LLC subsidiary entered into the U.S. Government Agreement (as defined below), which is a cooperative agreement with the U.S. government to expand our Sterile Injectables segment's fill-finish manufacturing production capacity and capabilities at our Rochester, Michigan plant to support the U.S. government's national defense efforts regarding production of critical medicines advancing pandemic preparation. For further discussion, refer to Note 16. Commitments and Contingencies in the Consolidated Financial Statements included in Part IV, Item 15 of this report.
- During the first quarter of 2022, multiple competitive generic alternatives to VASOSTRICT® were launched, beginning with a generic that was launched at risk and began shipping toward the end of January 2022. Since then, additional competitive alternatives entered the market, including authorized generics. These launches began to significantly impact both Endo's market share and product price toward the middle of the first quarter of 2022, and the effects of competition have since increased. Additionally, beginning late in the first quarter of 2022, COVID-19-related hospital utilization levels began to decline, resulting in significantly decreased market volumes for both branded and competing generic alternatives to VASOSTRICT®.
- In February 2022, we launched VASOSTRICT® in an RTU bottle, representing the first and only RTU formulation of the drug. The bottle formulation now represents a meaningful portion of the overall vasopressin market. Nevertheless, the factors described in the preceding bullet point could have a material adverse effect on our business, financial condition, results of operations and cash flows.

- In April 2022, we communicated the initiation of certain actions to streamline and simplify certain functions, including our commercial organization, to increase our overall organizational effectiveness and better align with current and future needs. In December 2022, we announced we would be taking certain additional actions to cease the production and sale of QWO® in light of market concerns about the extent and variability of bruising following initial treatment as well as the potential for prolonged skin discoloration. QWO® had been launched for the treatment of moderate to severe cellulite in the buttocks of adult women in March 2021. These actions are collectively referred to herein as the 2022 Restructuring Initiative. We have recorded and may continue to record certain charges to complete these actions in anticipation of realizing annualized cost savings. For further discussion of these actions, including a discussion of amounts recognized and information about any expected future charges, refer to Note 5. Restructuring in the Consolidated Financial Statements included in Part IV, Item 15 of this report.
- In May 2022, we announced that our EVL subsidiary had entered into an agreement to acquire six development-stage RTU injectable product candidates from Nevakar Injectables, Inc., a subsidiary of Nevakar, Inc., for an upfront cash payment of $35.0 million, which was recorded as an Acquired in-process research and development charge in the Consolidated Statements of Operations in the second quarter of 2022. For further discussion of this agreement, as well as a discussion of subsequent legal proceedings with Nevakar (as defined below) that affected both this agreement and a prior 2018 agreement with Nevakar, see Note 12. License, Collaboration and Asset Acquisition Agreements in the Consolidated Financial Statements included in Part IV, Item 15 of this report.
- In June 2022, we announced that our EVL subsidiary had entered into an agreement with TLC to commercialize TLC599. During the second quarter of 2022, we made an upfront cash payment of $30.0 million to TLC, which was recorded as an Acquired in-process research and development charge in the Consolidated Statements of Operations in the second quarter of 2022. For further discussion of this agreement, see Note 12. License, Collaboration and Asset Acquisition Agreements in the Consolidated Financial Statements included in Part IV, Item 15 of this report.
- Beginning in June 2022, we elected to enter certain 30-day grace periods related to senior notes interest payments that were originally due to be paid between June 30, 2022 and August 1, 2022. Certain of these payments were subsequently paid prior to the expiration of the applicable grace periods; others were not. Refer to Note 1. Description of Business and Note 15. Debt in the Consolidated Financial Statements included in Part IV, Item 15 of this report for further discussion.
- On the Petition Date, the Debtors filed voluntary petitions for relief under the Bankruptcy Code, which constituted an event of default that accelerated our obligations under substantially all of our then-outstanding debt instruments. However, section 362 of the Bankruptcy Code stays creditors from taking any action to enforce the related financial obligations and creditors' rights of enforcement in respect of the debt instruments are subject to the applicable provisions of the Bankruptcy Code. We are subject to risks and uncertainties associated with our ongoing bankruptcy proceedings, which could have a material adverse effect on our business, financial condition, results of operations and cash flows. Refer to Note 1. Description of Business, Note 2. Bankruptcy Proceedings and Note 15. Debt in the Consolidated Financial Statements included in Part IV, Item 15 of this report for further discussion.
- During the first quarter of 2023, a competitor launched an alternative generic version of varenicline tablets. This launch began to impact both Endo's market share and product price toward the middle of the first quarter of 2023, resulting in a decline in revenue for our Generic Pharmaceuticals segment. The effects of competition are likely to increase in future periods.
- In addition to our other legal proceedings, we, along with others, are the subject of various legal proceedings regarding the sale, marketing and/or distribution of prescription opioid medications, which are further discussed herein. Notwithstanding any relief that may be available as a result of our bankruptcy proceedings, it is possible that our legal proceedings, including those relating to opioid claims, could have a material adverse effect on our business, financial condition, results of operations and cash flows, including in the short term. For further discussion, refer to Note 1. Description of Business, Note 2. Bankruptcy Proceedings and Note 16. Commitments and Contingencies in the Consolidated Financial Statements included in Part IV, Item 15 of this report, as well as Part I, Item 1A. "Risk Factors."

CRITICAL ACCOUNTING ESTIMATES

The preparation of our Consolidated Financial Statements in conformity with U.S. generally accepted accounting principles (U.S. GAAP) requires us to make estimates and assumptions that affect the amounts and disclosures in our Consolidated Financial Statements, including the Notes thereto, and elsewhere in this report. For example, we are required to make significant estimates and assumptions related to revenue recognition, including sales deductions, long-lived assets, goodwill, other intangible assets, income taxes, contingencies, financial instruments, share-based compensation, liabilities subject to compromise and reorganization items, net, among others. Some of these estimates can be subjective and complex. Uncertainties related to the continued magnitude and duration of the COVID-19 pandemic, the extent to which it will impact our estimated future financial results, worldwide macroeconomic conditions including interest rates, employment rates, consumer spending, health insurance coverage, the speed of the anticipated recovery and governmental and business reactions to the pandemic, including any possible re-initiation of shutdowns or renewed restrictions, have increased the complexity of developing these estimates, including the allowance for expected credit losses and the carrying amounts of long-lived assets, goodwill and other intangible assets. Additionally, as a result of our ongoing bankruptcy proceedings, we may sell or otherwise dispose of or liquidate assets or settle liabilities for amounts other than those reflected in the accompanying Consolidated Financial Statements. The possibility or occurrence of any such actions could materially impact the amounts and classifications of such assets and liabilities reported in our Consolidated Balance Sheets. Furthermore, our ongoing bankruptcy proceedings and planned sale process have resulted in and are likely to continue to result in significant changes to our business, which could ultimately result in, among other things, asset impairment charges that may be material. Although we believe that our estimates and assumptions are reasonable, there may be other reasonable estimates or assumptions that differ significantly from ours. Further, our estimates and assumptions are based upon information available at the time they were made. Actual results may differ significantly from our estimates, including as a result of the uncertainties described in this report, those described in our other reports filed with the SEC or other uncertainties.

Accordingly, in order to understand our Consolidated Financial Statements, it is important to understand our critical accounting estimates. We consider an accounting estimate to be critical if both: (i) the accounting estimate requires us to make assumptions about matters that were highly uncertain at the time the accounting estimate was made and (ii) changes in the estimate that are reasonably likely to occur from period to period, or use of different estimates that we reasonably could have used in the current period, would have a material impact on our financial condition, results of operations or cash flows. Our most critical accounting estimates are described below.

Revenue recognition

With respect to contracts with commercial substance that establish payment terms and each party's rights regarding goods or services to be transferred, we recognize revenue when (or as) we satisfy our performance obligations for such contracts by transferring control of the underlying promised goods or services to our customers, to the extent collection of substantially all of the related consideration is probable. The amount of revenue we recognize reflects our estimate of the consideration we expect to be entitled to receive, subject to certain constraints, in exchange for such goods or services. This amount is referred to as the transaction price.

Our revenue consists almost entirely of sales of our products to customers, whereby we ship products to a customer pursuant to a purchase order. For contracts such as these, revenue is recognized when our contractual performance obligations have been fulfilled and control has been transferred to the customer pursuant to the contract's terms, which is generally upon delivery to the customer. The amount of revenue we recognize is equal to the fixed amount of the transaction price, adjusted for our estimates of a number of significant variable components including, but not limited to, estimates for chargebacks, rebates, sales incentives and allowances, DSA and other fees for services, returns and allowances, which we collectively refer to as sales deductions.

The Company utilizes the expected value method when estimating the amount of variable consideration to include in the transaction price with respect to each of the foregoing variable components and the most likely amount method when estimating the amount of variable consideration to include in the transaction price with respect to future potential milestone payments that do not qualify for the sales- and usage-based royalty exception. Variable consideration is included in the transaction price only to the extent it is probable that a significant revenue reversal will not occur when the uncertainty associated with the variable consideration is resolved. The variable component of the transaction price is estimated based on factors such as our direct and indirect customers' buying patterns and the estimated resulting contractual deduction rates, historical experience, specific known market events and estimated future trends, current contractual and statutory requirements, industry data, estimated customer inventory levels, current contract sales terms with our direct and indirect customers and other competitive factors. We subsequently review our estimates for sales deductions based on new or revised information that becomes available to us and make revisions to our estimates if and when appropriate. Refer to "Sales deductions" section below for additional information.

We believe that speculative buying of product, particularly in anticipation of possible price increases, has been the historical practice of certain of our customers. The timing of purchasing decisions made by wholesaler and large retail chain customers can materially affect the level of our sales in any particular period. Accordingly, our sales may not correlate to the number of prescriptions written for our products based on external third-party data.

We have entered into DSAs with certain of our significant wholesaler customers that obligate the wholesalers, in exchange for fees paid by us, to: (i) manage the variability of their purchases and inventory levels within specified limits based on product demand and (ii) provide us with specific services, including the provision of periodic retail demand information and current inventory levels for our pharmaceutical products held at their warehouse locations.

Sales deductions

As described above, the amount of revenue we recognize is equal to the fixed amount of the transaction price, adjusted for our estimates of variable consideration, including sales deductions. If the assumptions we use to calculate our estimates for sales deductions do not appropriately reflect future activity, our financial position, results of operations and cash flows could be materially impacted. The following table presents the activity and ending balances, excluding Discontinued operations, for our product sales provisions for the years ended December 31, 2022 and 2021 (in thousands):

	Returns and Allowances	Rebates	Chargebacks	Other Sales Deductions	Total
Balance, December 31, 2020	$ 207,916	$ 179,445	$ 190,528	$ 27,726	$ 605,615
Current year provision	81,944	619,279	2,265,277	126,080	3,092,580
Prior year provision	(16,313)	(6,481)	(153)	(911)	(23,858)
Payments or credits	(90,431)	(595,775)	(2,270,469)	(128,939)	(3,085,614)
Balance, December 31, 2021	$ 183,116	$ 196,468	$ 185,183	$ 23,956	$ 588,723
Current year provision	77,698	634,439	2,229,131	137,758	3,079,026
Prior year provision	(5,614)	(5,031)	(965)	(272)	(11,882)
Payments or credits	(88,034)	(612,600)	(2,238,647)	(116,429)	(3,055,710)
Balance, December 31, 2022	$ 167,166	$ 213,276	$ 174,702	$ 45,013	$ 600,157

Returns and Allowances

Consistent with industry practice, we maintain a return policy that allows our customers to return products within a specified period of time both subsequent to and, in certain cases, prior to the products' expiration dates. Our return policy generally allows customers to receive credit for expired products within six months prior to expiration and within between six months and one year after expiration. Our provision for returns and allowances consists of our estimates for future product returns, pricing adjustments and delivery errors. The primary factors we consider in estimating our potential product returns include:

- the shelf life or expiration date of each product;
- historical levels of expired product returns;
- external data with respect to inventory levels in the wholesale distribution channel;
- external data with respect to prescription demand for our products; and
- the estimated returns liability to be processed by year of sale based on analysis of lot information related to actual historical returns.

In determining our estimates for returns and allowances, we are required to make certain assumptions regarding the timing of the introduction of new products and the potential of these products to capture market share. In addition, we make certain assumptions with respect to the extent and pattern of decline associated with generic competition. To make these assessments, we utilize market data for similar products as analogs for our estimations. We use our best judgment to formulate these assumptions based on past experience and information available to us at the time. We continually reassess and make appropriate changes to our estimates and assumptions as new information becomes available to us.

Our estimate for returns and allowances may be impacted by a number of factors, but the principal factor relates to the level of inventory in the distribution channel. Where available, we utilize information received from our wholesaler customers about the quantities of inventory held, including the information received pursuant to DSAs, which we have not independently verified. For other customers, we have estimated inventory held based on buying patterns. In addition, we evaluate market conditions for products primarily through the analysis of wholesaler and other third-party sell-through data, as well as internally-generated information, to assess factors that could impact expected product demand at the estimate date. As of December 31, 2022, we believe that our estimates of the level of inventory held by our customers is within a reasonable range as compared to both historical amounts and expected demand for each respective product.

When we are aware of an increase in the level of inventory of our products in the distribution channel, we consider the reasons for the increase to determine whether we believe the increase is temporary or other-than-temporary. Increases in inventory levels assessed as temporary will not result in an adjustment to our provision for returns and allowances. Some of the factors that may be an indication that an increase in inventory levels will be temporary include:

- recently implemented or announced price increases for our products; and
- new product launches or expanded indications for our existing products.

Conversely, other-than-temporary increases in inventory levels may be an indication that future product returns could be higher than originally anticipated and, accordingly, we may need to adjust our provision for returns and allowances. Some of the factors that may be an indication that an increase in inventory levels will be other-than-temporary include:

- declining sales trends based on prescription demand;
- recent regulatory approvals to shorten the shelf life of our products, which could result in a period of higher returns related to older product still in the distribution channel;
- introduction of generic, OTC or other competing products;
- increasing price competition from competitors; and
- changes to the National Drug Codes (NDCs) of our products, which could result in a period of higher returns related to product with the old NDC, as our customers generally permit only one NDC per product for identification and tracking within their inventory systems.

Rebates

Our provision for rebates, sales incentives and other allowances can generally be categorized into the following four types:

- direct rebates;
- indirect rebates;
- governmental rebates, including those for Medicaid, Medicare and TRICARE, among others; and
- managed-care rebates.

We establish contracts with wholesalers, chain stores and indirect customers that provide for rebates, sales incentives, DSA fees and other allowances. Some customers receive rebates upon attaining established sales volumes. Direct rebates are generally rebates paid to direct purchasing customers based on a percentage applied to a direct customer's purchases from us, including fees paid to wholesalers under our DSAs, as described above. Indirect rebates are rebates paid to indirect customers that have purchased our products from a wholesaler or distributor under a contract with us.

We are subject to rebates on sales made under governmental and managed-care pricing programs based on relevant statutes with respect to governmental pricing programs and contractual sales terms with respect to managed-care providers and GPOs. For example, we are required to provide a discount on certain of our products to patients who fall within the Medicare Part D coverage gap, also referred to as the donut hole.

We participate in various federal and state government-managed programs whereby discounts and rebates are provided to participating government entities. For example, Medicaid rebates are amounts owed based upon contractual agreements or legal requirements with public sector (Medicaid) benefit providers after the final dispensing of the product by a pharmacy to a benefit plan participant. Medicaid reserves are based on expected payments, which are driven by patient usage, contract performance and field inventory that will be subject to a Medicaid rebate. Medicaid rebates are typically billed up to 180 days after the product is shipped, but can be as much as 270 days after the quarter in which the product is dispensed to the Medicaid participant. Periodically, we adjust the Medicaid rebate provision based on actual claims paid. Due to the delay in billing, adjustments to actual claims paid may incorporate revisions of this provision for several periods. Because Medicaid pricing programs involve particularly difficult interpretations of complex statutes and regulatory guidance, our estimates could differ from actual experience.

In determining our estimates for rebates, we consider the terms of our contracts and relevant statutes, together with information about sales mix (to determine which sales are subject to rebates and the amount of such rebates), historical relationships of rebates to revenues, past payment experience, estimated inventory levels of our customers and estimated future trends. Our provisions for rebates include estimates for both unbilled claims for end-customer sales that have already occurred and future claims that will be made when inventory in the distribution channel is sold through to end-customer plan participants. Changes in the level of utilization of our products through private or public benefit plans and GPOs will affect the amount of rebates that we owe.

Chargebacks

We market and sell products to both: (i) direct customers including wholesalers, distributors, warehousing pharmacy chains and other direct purchasing entities and (ii) indirect customers including independent pharmacies, non-warehousing chains, MCOs, GPOs, hospitals and other healthcare institutions and government entities. We enter into agreements with certain of our indirect customers to establish contract pricing for certain products. These indirect customers then independently select a wholesaler from which to purchase the products at these contracted prices. Alternatively, we may pre-authorize wholesalers to offer specified contract pricing to other indirect customers. Under either arrangement, we provide credit to the wholesaler for any difference between the contracted price with the indirect customer and the wholesaler's invoice price. Such credit is called a chargeback.

Our provision for chargebacks consists of our estimates for the credits described above. The primary factors we consider in developing and evaluating our provision for chargebacks include:

- the average historical chargeback credits;
- estimated future sales trends; and
- an estimate of the inventory held by our wholesalers, based on internal analysis of a wholesaler's historical purchases and contract sales.

Other sales deductions

We offer prompt-pay cash discounts to certain of our customers. Provisions for such discounts are estimated and recorded at the time of sale. We estimate provisions for cash discounts based on contractual sales terms with customers, an analysis of unpaid invoices and historical payment experience. Estimated cash discounts have historically been predictable and less subjective due to the limited number of assumptions involved, the consistency of historical experience and the fact that we generally settle these amounts upon receipt of payment by the customer.

Shelf-stock adjustments are credits issued to our customers to reflect decreases in the selling prices of our products. These credits are customary in the industry and are intended to reduce a customer's inventory cost to better reflect current market prices. The primary factors we consider when deciding whether to record a reserve for a shelf-stock adjustment include:

- the estimated number of competing products being launched as well as the expected launch date, which we determine based on market intelligence;
- the estimated decline in the market price of our product, which we determine based on historical experience and customer input; and
- the estimated levels of inventory held by our customers at the time of the anticipated decrease in market price, which we determine based upon historical experience and customer input.

Valuation of long-lived assets

As of December 31, 2022, our combined long-lived assets balance, including property, plant and equipment and finite-lived intangible assets, is approximately $2.2 billion. Our finite-lived intangible assets consist of license rights and developed technology.

Long-lived assets are generally initially recorded at fair value if acquired in a business combination, or at cost if otherwise. To the extent any such asset is deemed to have a finite life and to be held and used, it is amortized over its estimated useful life using either the straight-line method or, in the case of certain developed technology assets, an accelerated amortization model. The values of these various assets are subject to continuing scientific, medical and marketplace uncertainty. Factors giving rise to our initial estimate of useful lives are subject to change. Significant changes to any of these factors may result in adjustments to the useful life of the asset and an acceleration of related amortization expense, which could cause our net income and net income per share to decrease. Amortization expense is not recorded on assets held for sale.

Long-lived assets are assessed for impairment whenever events or changes in circumstances indicate the assets may not be recoverable. Recoverability of an asset that will continue to be used in our operations is measured by comparing the carrying amount of the asset to the forecasted undiscounted future cash flows related to the asset. In the event the carrying amount of the asset exceeds its undiscounted future cash flows and the carrying amount is not considered recoverable, impairment may exist. An impairment loss, if any, is measured as the excess of the asset's carrying amount over its fair value, generally based on a discounted future cash flow method, independent appraisals or offers from prospective buyers. An impairment loss would be recognized in the Consolidated Statements of Operations in the period that the impairment occurs.

In the case of long-lived assets to be disposed of by sale or otherwise, including assets held for sale, the assets and the associated liabilities to be disposed of together as a group in a single transaction (the disposal group) are measured at the lower of their carrying amount or fair value less cost to sell. Prior to disposal, losses are recognized for any initial or subsequent write-down to fair value less cost to sell, while gains are recognized for any subsequent increase in fair value less cost to sell, but not in excess of any cumulative losses previously recognized. Any gains or losses not previously recognized that result from the sale of a disposal group shall be recognized at the date of sale.

As a result of the significance of our long-lived assets, any recognized losses could have a material adverse impact on our financial position and results of operations.

Our reviews of long-lived assets during the two years ended December 31, 2022 resulted in certain impairment charges. The majority of these charges related to finite-lived intangible assets and certain assets associated with disposal groups, which are further described in Note 11. Goodwill and Other Intangibles and Note 4. Discontinued Operations and Asset Sales, respectively, in the Consolidated Financial Statements included in Part IV, Item 15 of this report. Our impairment charges relating to long-lived assets were generally based on fair value estimates determined using discounted cash flow models or, in the case of disposal groups, a market approach. When testing a long-lived asset using a discounted cash flow model, we utilize assumptions related to the future operating performance of the corresponding product based on management's annual and ongoing budgeting, forecasting and planning processes, which represent our best estimate of future cash flows. These estimates are subject to many assumptions, such as the economic environment in which our segments operate, demand for our products, competitor actions and factors which could affect our tax rate. Estimated future pre-tax cash flows are adjusted for taxes using a market participant tax rate and discounted to present value using a market participant weighted average cost of capital. Financial and credit market volatility directly impacts certain inputs and assumptions used to develop the weighted average cost of capital such as the risk-free interest rate, industry beta, debt interest rate and certain capital structure considerations. These assumptions are based on significant inputs and judgments not observable in the market, and thus represent Level 3 measurements within the fair value hierarchy. The use of different inputs and assumptions would increase or decrease our estimated discounted future cash flows, the resulting estimated fair values and the amounts of our related impairments, if any. The discount rates applied to intangible long-lived assets impaired in 2022 ranged from 9.5% to 12.0%.

Events giving rise to impairment are an inherent risk in the pharmaceutical industry and cannot be predicted with certainty. Factors that we consider in deciding when to perform an impairment review include significant under-performance of a product line in relation to expectations, competitive events affecting the expected future performance of a product line, significant negative industry or economic trends and significant changes or planned changes in our use of the assets.

Each category of long-lived intangible assets is described further below.

Developed Technology. Our developed technology assets subject to amortization have useful lives ranging from 6 years to 16 years, with a weighted average useful life of approximately 12 years. We determine amortization periods and methods of amortization for developed technology assets based on our assessment of various factors impacting estimated useful lives and the timing and extent of estimated cash flows of the acquired assets, including the strength of the intellectual property protection of the product (if applicable), contractual terms and various other competitive and regulatory issues.

License Rights. Our license rights subject to amortization have useful lives ranging from 7 years to 15 years, with a weighted average useful life of approximately 14 years. We determine amortization periods for licenses based on our assessment of various factors including the expected launch date of the product, the strength of the intellectual property protection of the product (if applicable), contractual terms and various other competitive, developmental and regulatory issues.

As of December 31, 2022, the carrying amount of our intangible assets associated with developed technology and license rights totaled approximately $1.7 billion. As a result, if the assumptions used in our impairment tests change, it is possible that material impairment charges could be recorded in future periods.

Goodwill and indefinite-lived intangible assets

As of December 31, 2022, our goodwill balance is approximately $1.4 billion and we have no indefinite-lived intangible assets.

Goodwill and, if applicable, indefinite-lived intangible assets are tested for impairment annually, as of October 1, and when events or changes in circumstances indicate that the asset might be impaired.

We perform the goodwill impairment test by estimating the fair value of the reporting units using an income approach that utilizes a discounted cash flow model or, where appropriate, a market approach. Any goodwill impairment charge we recognize for a reporting unit is equal to the lesser of: (i) the total goodwill allocated to that reporting unit and (ii) the amount by which that reporting unit's carrying amount exceeds its fair value.

Similarly, if applicable, we perform our indefinite-lived intangible asset impairment tests by comparing the fair value of each intangible asset with its carrying amount. We estimate the fair values of our indefinite-lived intangible assets using an income approach that utilizes a discounted cash flow model. If the carrying amount of an indefinite-lived intangible asset exceeds its fair value, an impairment loss is recognized in an amount equal to that excess.

The discounted cash flow models reflect our estimates of future cash flows and other factors including estimates of: (i) future operating performance, including future sales, long-term growth rates, gross margins, operating expenses, discount rates and the probability of achieving the estimated cash flows, and (ii) future economic conditions, all of which may differ from actual future cash flows.

Assumptions related to future operating performance are based on management's annual and ongoing budgeting, forecasting and planning processes, which represent our best estimate of future cash flows. These estimates are subject to many assumptions, such as the economic environment in which our segments operate, demand for our products, competitor actions and factors which could affect our tax rate. Estimated future pre-tax cash flows are adjusted for taxes using a market participant tax rate and discounted to present value using a market participant weighted average cost of capital. Financial and credit market volatility directly impacts certain inputs and assumptions used to develop the weighted average cost of capital such as the risk-free interest rate, industry beta, debt interest rate and certain capital structure considerations. Where appropriate, the weighted average cost of capital may also incorporate certain risk premiums, such as a company-specific risk premium (CSRP), which represents the incremental return that investors may require to compensate for the risks, uncertainties and variability in our estimated future cash flows. These assumptions are based on significant inputs and judgments not observable in the market, and thus represent Level 3 measurements within the fair value hierarchy. The use of different inputs and assumptions would increase or decrease our estimated discounted future cash flows, the resulting estimated fair values and the amounts of our related impairments, if any.

In order to assess the reasonableness of the calculated fair values of our reporting units, we also compare the sum of the reporting units' fair values to Endo's market capitalization, together with the aggregate estimated fair value of its debt, and/or observable bids for the Company, such as the Stalking Horse Bid (as defined and further described in Note 2. Bankruptcy Proceedings in the Consolidated Financial Statements included in Part IV, Item 15 of this report). We use this comparison to calculate an implied control premium (the excess sum of the reporting units' fair values over Endo's market capitalization, together with the aggregate estimated fair value of its debt, and/or observable bids) or an implied control discount (the excess of Endo's market capitalization, together with the aggregate estimated fair value of its debt, and/or observable bids over the sum of the reporting units' fair values). The Company evaluates the implied control premium or discount by comparing it to control premiums or discounts of recent comparable market transactions, as applicable. If the control premium or discount is not reasonable in light of comparable recent transactions, or recent movements in the Company's share price and/or the aggregate estimated fair value of its debt, we reevaluate the fair value estimates of the reporting units to determine whether it is appropriate to adjust discount rates and/or other assumptions. This re-evaluation could correlate to different implied fair values for certain or all of the Company's reporting units.

As further described in Note 11. Goodwill and Other Intangibles in the Consolidated Financial Statements included in Part IV, Item 15 of this report, Endo performed its annual impairment tests as of October 1, 2022. For the purposes of the 2022 annual tests, the Company had two reporting units with goodwill: Branded Pharmaceuticals and Sterile Injectables; the Company did not have any indefinite-lived intangible assets.

The discount rates used in the October 1, 2022 goodwill tests were 15.0% and 19.5% for the Branded Pharmaceuticals and Sterile Injectables reporting units, respectively, compared to: (i) 15.0% and 19.5%, respectively, used in the interim goodwill tests performed in the third quarter of 2022; (ii) 13.5% and 18.5%, respectively, used in the interim goodwill tests performed in the second quarter of 2022; and (iii) 14.5% and 11.0%, respectively, used in the October 1, 2021 goodwill tests. The discount rates used in these 2022 goodwill tests reflect certain increases in the CSRP compared to the October 1, 2021 tests, representing increased risks and uncertainties in the underlying cash flows, including those related to: (i) our ability to identify, develop and launch new product candidates, particularly in our Sterile Injectables reporting unit and (ii) risks and uncertainties associated with our ongoing bankruptcy proceedings. We believe the discount rates and other inputs and assumptions used in these various tests were consistent with those that a market participant would have used.

We recorded goodwill impairment charges of $1,748.0 million and $97.0 million, respectively, in connection with our second- and third-quarter 2022 interim impairment tests of our Sterile Injectables reporting unit. No impairment charges were recorded for our Branded Pharmaceuticals reporting unit as a result of these tests.

We completed our annual goodwill impairment tests on October 1, 2022; no additional impairments were recorded in connection with these tests. A 50 basis point increase in the assumed discount rate utilized in the Branded Pharmaceuticals test would not have changed the outcome of that test; however, a 50 basis point increase in the assumed discount rate utilized in the Sterile Injectables test would have resulted in a goodwill impairment charge for this reporting unit of approximately $45 million.

We performed an additional interim goodwill impairment test for our Sterile Injectables reporting unit as of December 31, 2022 based, in part, on updates made to our estimates of future cash flows following the completion of our annual enterprise-wide long-term strategic planning process beginning in late fourth-quarter 2022 and concluding in February 2023, which is further described in Note 11. Goodwill and Other Intangibles in the Consolidated Financial Statements included in Part IV, Item 15 of this report. The discount rate used in this test was 14.5%. We believe this discount rate and the other inputs and assumptions used to estimate fair value were consistent with those that a market participant would have used in light of the degree of risk associated with the updated estimated future cash flows used in this impairment test as compared to the October 1, 2022 tests. As a result of the December 31, 2022 test, we determined that there was no impairment of goodwill. A 50 basis point increase in the assumed discount rate utilized in this test would have resulted in a goodwill impairment charge for this reporting unit of approximately $15 million.

Additional information about our impairment tests is provided in Note 11. Goodwill and Other Intangibles in the Consolidated Financial Statements included in Part IV, Item 15 of this report.

As of December 31, 2022, our Branded Pharmaceuticals and Sterile Injectables reporting units had remaining goodwill of approximately $0.8 billion and $0.5 billion, respectively. As a result, if the assumptions used in our impairment tests change, it is possible that additional impairment charges could be recorded in future periods and that these charges could be material.

Each of our reporting units is subject to various risks and uncertainties, including those described above and in Note 11. Goodwill and Other Intangibles in the Consolidated Financial Statements included in Part IV, Item 15 of this report. If actual results for our reporting units differ from our expectations, as a result of these or other risks and uncertainties, and/or if we make related changes to our assumptions for these reporting units, the estimated future revenues and cash flows could be significantly reduced, which could ultimately result in goodwill impairment charges that may be material.

Income taxes

Our income tax expense, deferred tax assets and liabilities, income tax payable and reserves for unrecognized tax benefits reflect our best assessment of estimated current and future taxes to be paid. We are subject to income taxes in the U.S. and numerous other jurisdictions in which we operate. Significant judgments and estimates are required in determining the consolidated income tax expense or benefit for financial statement purposes. Deferred income taxes arise from temporary differences, which result in future taxable or deductible amounts, between the tax basis of assets and liabilities and the corresponding amounts reported in our Consolidated Financial Statements. In assessing the ability to realize deferred tax assets, we consider, when appropriate, future taxable income by tax jurisdiction and tax planning strategies. Where appropriate, we record a valuation allowance to reduce our net deferred tax assets to equal an amount that is more likely than not to be realized. In projecting future taxable income, we consider historical results, adjusted in certain cases for the results of discontinued operations, changes in tax laws or nonrecurring transactions. We incorporate assumptions about the amount of future earnings within a specific jurisdiction's pretax income, adjusted for material changes included in business operations. The assumptions about future taxable income require significant judgment and, while these assumptions rely heavily on estimates, such estimates are consistent with the plans we are using to manage the underlying business. Future changes in tax laws and rates, including administrative or regulatory guidance, could affect recorded deferred tax assets and liabilities. Any adjustments to these estimates will generally be recorded as an income tax expense or benefit in the period the adjustment is determined.

The calculation of our tax liabilities often involves dealing with uncertainties in the application of complex tax laws and regulations in a multitude of jurisdictions across our global operations. A benefit from an uncertain tax position may be recognized when it is more likely than not that the position will be sustained on the basis of the technical merits upon examination, including resolutions of any related appeals or litigation processes. We first record unrecognized tax benefits as liabilities and then adjust these liabilities when our judgment changes as a result of the evaluation of new information not previously available at the time of establishing the liability. Because of the complexity of some of these uncertainties, the ultimate resolution may result in a payment, potentially including interest and penalties, that is materially different from our current estimate of the unrecognized tax benefit liabilities. These differences, along with any related interest and penalties, will generally be reflected as increases or decreases to income tax expense in the period in which new information becomes available.

We make an evaluation at the end of each reporting period as to whether or not some or all of the undistributed earnings of our subsidiaries are indefinitely reinvested. Refer to Note 21. Income Taxes in the Consolidated Financial Statements included in Part IV, Item 15 of this report for information about our evaluation for the current reporting period and certain associated risks and uncertainties.

Contingencies

Material legal proceedings involving the Company are discussed in Note 16. Commitments and Contingencies in the Consolidated Financial Statements included in Part IV, Item 15 of this report. Contingent accruals and legal settlements are recorded in the Consolidated Statements of Operations as Litigation-related and other contingencies, net (or as Discontinued operations, net of tax in the case of vaginal mesh matters) when the Company determines that a loss is both probable and reasonably estimable. Legal fees and other expenses related to litigation are expensed as incurred and are generally included in Selling, general and administrative expenses in the Consolidated Statements of Operations (or as Discontinued operations, net of tax in the case of vaginal mesh matters).

Due to the fact that legal proceedings and other contingencies are inherently unpredictable, our estimates of the probability and amount of any such liabilities involve significant judgment regarding future events. The factors we consider in developing our liabilities for legal proceedings include the merits and jurisdiction of the proceeding, the nature and the number of other similar current and past proceedings, the nature of the product and the current assessment of the science subject to the proceeding, if applicable, and the likelihood of the conditions of settlement being met.

In order to evaluate whether a claim is probable of loss, we may rely on certain information about the claim. Without access to and review of such information, we may not be in a position to determine whether a loss is probable. Further, the timing and extent to which we obtain any such information, and our evaluation thereof, is often impacted by items outside of our control including, without limitation, the normal cadence of the litigation process and the provision of claim information to us by plaintiff's counsel. The amount of our liabilities for legal proceedings may change as we receive additional information and/or become aware of additional asserted or unasserted claims. Additionally, there is a possibility that we will suffer adverse decisions or verdicts of substantial amounts or that we will enter into additional monetary settlements, either of which could be in excess of amounts previously accrued for. Any changes to our liabilities for legal proceedings could have a material adverse effect on our business, financial condition, results of operations and cash flows.

As of December 31, 2022, our accrual for loss contingencies totaled $820.8 million, the most significant components of which relate to: (i) various opioid-related matters as further described herein and (ii) product liability and related matters associated with transvaginal surgical mesh products, which we have not sold since March 2016. Although we believe there is a possibility that a loss in excess of the amount recognized exists, we are unable to estimate the possible loss or range of loss in excess of the amount recognized at this time. As of December 31, 2022, our entire accrual for loss contingencies is classified as Liabilities subject to compromise in the Consolidated Balance Sheets. As a result of the automatic stay under the Bankruptcy Code and the uncertain treatment of these liabilities pursuant to a chapter 11 plan or otherwise, the timing and amount of payment, if any, related to the amounts accrued for loss contingencies is uncertain.

Liabilities subject to compromise

For periods beginning with the third quarter of 2022, pre-petition unsecured and undersecured claims related to the Debtors that may be impacted by the bankruptcy reorganization process have been classified as Liabilities subject to compromise in the Consolidated Balance Sheets. Liabilities subject to compromise include pre-petition liabilities for which there is uncertainty about whether such pre-petition liabilities could be impaired as a result of the Chapter 11 Cases. Liabilities subject to compromise are recorded at the expected amount of the total allowed claim, even if they may ultimately be settled for different amounts.

The determination of how liabilities will ultimately be settled or treated cannot be made until approved by the Bankruptcy Court. Therefore, the amounts classified as Liabilities subject to compromise are preliminary and may be subject to future adjustments as a result of, among other things, the possibility or occurrence of certain Bankruptcy Court actions, further developments with respect to disputed claims, any rejection by us of executory contracts and/or any payments by us of amounts classified as Liabilities subject to compromise, which may be allowed in certain limited circumstances. Amounts are also subject to adjustments if we make changes to our assumptions or estimates related to claims as additional information becomes available to us including, without limitation, those related to the expected amounts of allowed claims, the value of any collateral securing claims and the secured status of claims. Such adjustments may be material.

RESULTS OF OPERATIONS

Consolidated Results Review

The following table displays our revenue, gross margin, gross margin percentage and other pre-tax expense or income for the years ended December 31, 2022 and 2021 (dollars in thousands):

	2022	2021	% Change 2022 vs. 2021
Total revenues, net	$ 2,318,875	$ 2,993,206	(23)%
Cost of revenues	1,092,499	1,221,064	(11)%
Gross margin	$ 1,226,376	$ 1,772,142	(31)%
Gross margin percentage	*52.9 %*	*59.2 %*	
Selling, general and administrative	777,169	861,760	(10)%
Research and development	128,033	123,440	4 %
Acquired in-process research and development	68,700	25,120	NM
Litigation-related and other contingencies, net	478,722	345,495	39 %
Asset impairment charges	2,142,746	414,977	NM
Acquisition-related and integration items, net	408	(8,379)	NM
Interest expense, net	349,776	562,353	(38)%
Loss on extinguishment of debt	—	13,753	(100)%
Reorganization items, net	202,978	—	NM
Other income, net	(34,054)	(19,774)	72 %
Loss from continuing operations before income tax	$ (2,888,102)	$ (546,603)	NM

NM indicates that the percentage change is not meaningful or is greater than 100%

Total revenues, net. Total revenues in 2022 were $2,318.9 million compared to $2,993.2 million in 2021 as revenue decreases related to VASOSTRICT® and certain other products in our Sterile Injectables segment, as well as our Branded Pharmaceuticals and International Pharmaceuticals segments, were partially offset by increased revenues from our Generic Pharmaceuticals segment. Our revenues are further disaggregated and described below under the heading "Business Segment Results Review."

Cost of revenues and gross margin percentage. During the years ended December 31, 2022 and 2021, Cost of revenues includes certain amounts that impact its comparability among periods, as well as the comparability of gross margin percentage, including amortization expense and amounts related to continuity and separation benefits, cost reductions and strategic review initiatives. The following table summarizes such amounts (in thousands):

	2022	2021
Amortization of intangible assets (1)	$ 337,311	$ 372,907
Amounts related to continuity and separation benefits, cost reductions and strategic review initiatives (2)	$ 61,806	$ 9,058

(1) Amortization expense fluctuates based on changes in the total amount of amortizable intangible assets and the rate of amortization in effect for each intangible asset, both of which can vary based on factors such as the amount and timing of acquisitions, dispositions, asset impairment charges, transfers between indefinite- and finite-lived intangibles assets, changes in foreign currency rates and changes in the composition of our intangible assets impacting the weighted average useful lives and amortization methodologies being utilized The decrease in 2022 was primarily driven by prior asset impairment charges and decreases in the rate of amortization expense for certain assets

(2) Amounts include, among other things, certain accelerated depreciation charges, inventory adjustments and net employee separation, continuity and other benefit-related costs, including amounts related to restructurings For further discussion of our restructuring initiatives, including a discussion of amounts recognized and information about any expected future charges, refer to Note 4 Discontinued Operations and Asset Sales and Note 5 Restructuring in the Consolidated Financial Statements included in Part IV, Item 15 of this report

The decrease in Cost of revenues in 2022 was primarily due to decreased revenues and decreased amortization expense, partially offset by unfavorable changes in product mix resulting primarily from decreased VASOSTRICT® revenues, as well as increased costs for amounts related to continuity and separation benefits, cost reductions and strategic review initiatives.

The decrease in gross margin percentage in 2022 was primarily due to unfavorable changes in product mix resulting primarily from decreased VASOSTRICT® revenues.

Selling, general and administrative expenses. The decrease in 2022 was primarily due to decreased costs associated with our commercial investment in QWO® and certain legal matters. Additionally, in 2022, Selling, general and administrative expenses reflected the recovery of certain previously-incurred opioid-related legal expenses. These decreases were partially offset by increased Selling, general and administrative expenses associated with our investment in consumer marketing efforts supporting XIAFLEX® and certain strategic review initiatives, restructuring and/or other cost reduction initiatives, including costs incurred in connection with our bankruptcy proceedings, which are included in Selling, general and administrative expenses until the Petition Date and in Reorganization items, net thereafter. Refer to Note 5. Restructuring in the Consolidated Financial Statements included in Part IV, Item 15 of this report for further discussion of certain restructuring initiatives, including a discussion of amounts recognized and information about any expected future charges.

R&D expenses. Our R&D efforts are focused on the development of a diversified portfolio of innovative and clinically differentiated product candidates. The amount of R&D expense we record in any period varies depending on the nature and stage of development of our R&D programs, certain of which are further described below.

We continue to invest in our Branded Pharmaceuticals segment. In early 2020, we announced that we had initiated our XIAFLEX® development program for the treatment of plantar fibromatosis, for which we anticipate Phase 2 top-line data by the end of the first quarter of 2023. We also initiated a proof-of-concept study in plantar fasciitis during the fourth quarter of 2022. Additionally, until late 2022, we had been advancing our development programs for QWO®, which was launched in March 2021 for the treatment of moderate to severe cellulite in the buttocks of adult women. However, as further discussed in Note 5. Restructuring in the Consolidated Financial Statements included in Part IV, Item 15 of this report, in December 2022, we announced we would be ceasing the production and sale of QWO® in light of market concerns about the extent and variability of bruising following initial treatment as well as the potential for prolonged skin discoloration.

We expect to continue to focus investments in RTU and other product candidates in our Sterile Injectables segment, potentially including acquisitions and/or license and commercialization agreements such as the 2022 Nevakar Agreement that is further described in Note 12. License, Collaboration and Asset Acquisition Agreements in the Consolidated Financial Statements included in Part IV, Item 15 of this report.

The increase in R&D expense in 2022 was primarily driven by increased costs associated with our XIAFLEX® development programs, certain restructuring and other cost reduction initiatives and certain post-marketing commitments. These increases were partially offset by decreased costs associated with QWO®, including as a result of actions taken in connection with the discontinuation of QWO® discussed above. Refer to Note 5. Restructuring in the Consolidated Financial Statements included in Part IV, Item 15 of this report for further discussion of certain restructuring initiatives, including a discussion of amounts recognized and information about any expected future charges.

As our development programs progress, it is possible that our R&D expenses could increase.

Acquired in-process research and development. Acquired in-process research and development charges are generally recognized in periods in which in-process research and development assets (with no alternative future use in other research and development projects) are acquired from third parties in connection with an asset acquisition, or when costs are incurred (up to the point of regulatory approval) for upfront or milestone payments to third parties associated with in-process research and development. The increase in Acquired in-process research and development charges in 2022 was primarily driven by the incurrence, during the second quarter of 2022, of expenses related to upfront payments associated with the 2022 Nevakar Agreement and the TLC Agreement of $35.0 million and $30.0 million, respectively, which are further described in Note 12. License, Collaboration and Asset Acquisition Agreements in the Consolidated Financial Statements included in Part IV, Item 15 of this report. This increase was partially offset by the incurrence, during 2021, of approximately $25.1 million of expenses, which primarily related to upfront payments associated with various license agreements. To the extent we enter into agreements to acquire in-process research and development in the future and/or incur expenses related to upfront or milestone payments to third parties associated with existing or potential future agreements, Acquired in-process research and development charges could increase in the future, and the amounts of any increases could be material.

Litigation-related and other contingencies, net. Included within Litigation-related and other contingencies, net are changes to our accruals for litigation-related charges. Our material legal proceedings and other contingent matters are described in more detail in Note 16. Commitments and Contingencies in the Consolidated Financial Statements included in Part IV, Item 15 of this report. Notwithstanding any relief that may be available as a result of our bankruptcy proceedings, it is possible that our legal proceedings, including those relating to opioid claims, could have a material adverse effect on our business, financial condition, results of operations and cash flows, including in the short term. For further discussion, refer to Note 1. Description of Business, Note 2. Bankruptcy Proceedings and Note 16. Commitments and Contingencies in the Consolidated Financial Statements included in Part IV, Item 15 of this report.

Asset impairment charges. The following table presents the components of our total Asset impairment charges for the years ended December 31, 2022 and 2021 (in thousands):

	2022	2021
Goodwill impairment charges	$ 1,845,000	$ 363,000
Other intangible asset impairment charges	288,701	7,811
Property, plant and equipment impairment charges	9,045	2,011
Disposal group impairment charges	—	42,155
Total asset impairment charges	$ 2,142,746	$ 414,977

For additional information, refer to Note 4. Discontinued Operations and Asset Sales, Note 5. Restructuring, Note 7. Fair Value Measurements, Note 9. Leases, Note 10. Property, Plant and Equipment and Note 11. Goodwill and Other Intangibles in the Consolidated Financial Statements included in Part IV, Item 15 of this report, as well as the "CRITICAL ACCOUNTING ESTIMATES" section herein.

Acquisition-related and integration items, net. Acquisition-related and integration items, net primarily consist of the net expense (benefit) from changes in the fair value of acquisition-related contingent consideration liabilities resulting from changes to our estimates regarding the timing and amount of the future revenues of the underlying products and changes in other assumptions impacting the probability of incurring, and extent to which we could incur, related contingent obligations. See Note 7. Fair Value Measurements in the Consolidated Financial Statements included in Part IV, Item 15 of this report for further discussion of our acquisition-related contingent consideration.

Interest expense, net. The components of Interest expense, net for the years ended December 31, 2022 and 2021 are as follows (in thousands):

	2022	2021
Interest expense	$ 350,740	$ 562,937
Interest income	(964)	(584)
Interest expense, net	$ 349,776	$ 562,353

The decrease in interest expense in 2022 was primarily attributable to the fact that we ceased the recognition of interest expense related to our indebtedness beginning on the Petition Date as a result of the Chapter 11 Cases. Additionally, when compared to the prior year period, there have been decreases to interest expense resulting from reductions in the aggregate principal amount of our indebtedness, which were primarily attributable to the partial repayment of the Revolving Credit Facility in October 2021, the January 2022 Senior Notes Repayments and certain quarterly payments made on the Term Loan Facility. These decreases in interest expense were partially offset by increases in the weighted average interest rate applicable to our total indebtedness through the Petition Date. Beginning during the third quarter of 2022, we also became obligated to make certain adequate protection payments as a result of the Chapter 11 Cases, which are currently being accounted for as a reduction of the carrying amount of the related debt instruments. Some or all of the adequate protection payments may later be recharacterized as interest expense depending upon certain developments in the Chapter 11 Cases, which could result in increases in interest expense in future periods that may be material. Refer to Note 15. Debt in the Consolidated Financial Statements included in Part IV, Item 15 of this report for further discussion.

Interest income varies primarily based on the amounts of our interest-bearing investments, such as money market funds, as well as changes in the corresponding interest rates.

Loss on extinguishment of debt. The amount in 2021 relates to the March 2021 Refinancing Transactions. Refer to Note 15. Debt in the Consolidated Financial Statements included in Part IV, Item 15 of this report for further discussion.

Reorganization items, net. Amounts relate to the net expense or income recognized during our bankruptcy proceedings required to be presented as Reorganization items, net under *Accounting Standards Codification Topic 852, Reorganizations* (ASC 852). Refer to Note 2. Bankruptcy Proceedings in the Consolidated Financial Statements included in Part IV, Item 15 of this report for further details. Costs related to our bankruptcy proceedings that were incurred prior to the Petition Date are generally reflected as Selling, general and administrative expenses in our Consolidated Statements of Operations. We expect to continue to incur significant expenses in connection with our ongoing bankruptcy proceedings and certain related transactions and it is possible that such costs will increase over time, particularly if we incur certain associated success-related and/or other contingent fees, which could be significant. In addition, the longer the Chapter 11 Cases continue, the higher our expenses for these matters could be.

Other income, net. The components of Other income, net for the years ended December 31, 2022 and 2021 are as follows (in thousands):

	2022	2021
Net gain on sale of business and other assets	$ (26,183)	$ (4,516)
Foreign currency (gain) loss, net	(2,087)	1,253
Net loss from our investments in the equity of other companies	378	453
Other miscellaneous, net	(6,162)	(16,964)
Other income, net	$ (34,054)	$ (19,774)

For additional information on the components of Other income, net, refer to Note 20. Other Income, Net in the Consolidated Financial Statements included in Part IV, Item 15 of this report.

Income tax expense (benefit). The following table displays our Loss from continuing operations before income tax, Income tax expense and Effective tax rate for the years ended December 31, 2022 and 2021 (dollars in thousands):

	2022	2021
Loss from continuing operations before income tax	$ (2,888,102)	$ (546,603)
Income tax expense	$ 21,516	$ 22,478
Effective tax rate	*(0.7)%*	*(4.1)%*

Our tax rate is affected by recurring items, such as tax rates in non-U.S. jurisdictions as compared to the notional U.S. federal statutory tax rate, and the relative amount of income or loss in those various jurisdictions. It is also impacted by certain items that may occur in any given period, but are not consistent from period to period.

The change in income tax expense in 2022 compared to the 2021 income tax expense primarily relates to an increase in accrued interest on uncertain tax positions and changes in the geographic mix of pre-tax earnings. For additional discussion of the effective tax rate, see Note 21. Income Taxes in the Consolidated Financial Statements included in Part IV, Item 15 of this report.

As previously disclosed, the Company concluded that there was substantial doubt about its ability to continue as a going concern within one year after the date of issuance of the Condensed Consolidated Financial Statements included in the Quarterly Report on Form 10-Q for the quarterly period ended June 30, 2022 filed with the SEC on August 9, 2022 (the Second-Quarter 2022 Form 10-Q). The Company considered this in determining that certain net deferred tax assets were no longer more likely than not realizable. As a result, an immaterial increase in valuation allowance on the Company's net deferred tax assets was recorded in various jurisdictions during the second quarter of 2022.

The Company maintains a full valuation allowance against the net deferred tax assets in the U.S., Luxembourg, Ireland and certain other foreign tax jurisdictions as of December 31, 2022. It is possible that within the next 12 months there may be sufficient positive evidence to release a portion or all of the valuation allowance. Release of these valuation allowances would result in a benefit to income tax expense for the period the release is recorded, which could have a material impact on net earnings. The timing and amount of the potential valuation allowance release are subject to significant management judgment and prospective earnings.

We are incorporated in Ireland and also maintain subsidiaries in, among other jurisdictions, the U.S., Canada, India, the United Kingdom and Luxembourg. The IRS and other taxing authorities may continue to challenge our tax positions. The IRS presently is examining certain of our subsidiaries' U.S. income tax returns for fiscal years ended between December 31, 2011 and December 31, 2015 and, in connection with those examinations, is reviewing our tax positions related to, among other things, certain intercompany arrangements, including the level of profit earned by our U.S. subsidiaries pursuant to such arrangements, and a product liability loss carryback claim. For additional information, including a discussion of related recent developments and their potential impact on us, refer to Note 21. Income Taxes in the Consolidated Financial Statements included in Part IV, Item 15 of this report.

During the third quarter of 2020, the IRS opened an examination into certain of our subsidiaries' U.S. income tax returns for fiscal years ended between December 31, 2016 and December 31, 2018. The IRS will likely examine our tax returns for other fiscal years and/or for other tax positions. Similarly, other tax authorities are currently examining our non-U.S. tax returns. Additionally, other jurisdictions where we are not currently under audit remain subject to potential future examinations. Such examinations may lead to proposed or actual adjustments to our taxes that may be material, individually or in the aggregate. See the risk factor "The IRS and other taxing authorities may continue to challenge our tax positions and we may not be able to successfully maintain such positions" in Part I, Item 1A of this report for more information.

Additionally, as further discussed in Note 21. Income Taxes in the Consolidated Financial Statements included in Part IV, Item 15 of this report, the IRS has filed multiple proofs of claim against several of the Debtors in connection with our ongoing bankruptcy proceedings.

For additional information on our income taxes, see Note 21. Income Taxes in the Consolidated Financial Statements included in Part IV, Item 15 of this report.

Discontinued operations, net of tax. The operating results of the Company's Astora business, which the Board resolved to wind down in 2016, are reported as Discontinued operations, net of tax in the Consolidated Statements of Operations for all periods presented. The following table provides the operating results of Astora Discontinued operations, net of tax, for the years ended December 31, 2022 and 2021 (in thousands):

	2022	2021
Litigation-related and other contingencies, net	$ —	$ 25,000
Loss from discontinued operations before income taxes	$ (15,543)	$ (49,594)
Income tax benefit	$ (2,056)	$ (5,430)
Discontinued operations, net of tax	$ (13,487)	$ (44,164)

Amounts included in the Litigation-related and other contingencies, net line of the table above are for mesh-related litigation. The remaining pre-tax amounts in 2022 and 2021 were primarily related to mesh-related legal defense costs and certain other items. For additional discussion of mesh-related matters, refer to Note 16. Commitments and Contingencies in the Consolidated Financial Statements included in Part IV, Item 15 of this report.

Business Segment Results Review

Revenues, net. The following table displays our revenue by reportable segment for the years ended December 31, 2022 and 2021 (dollars in thousands):

	2022	2021	% Change 2022 vs. 2021
Branded Pharmaceuticals	$ 851,142	$ 893,617	(5)%
Sterile Injectables	589,633	1,266,097	(53)%
Generic Pharmaceuticals	795,457	740,586	7 %
International Pharmaceuticals (1)	82,643	92,906	(11)%
Total net revenues from external customers	$ 2,318,875	$ 2,993,206	(23)%

(1) Revenues generated by our International Pharmaceuticals segment are primarily attributable to external customers located in Canada

Branded Pharmaceuticals. The following table displays the significant components of our Branded Pharmaceuticals revenues from external customers for the years ended December 31, 2022 and 2021 (dollars in thousands):

	2022	2021	% Change 2022 vs. 2021
Specialty Products:			
XIAFLEX®	$ 438,680	$ 432,344	1 %
SUPPRELIN® LA	113,011	114,374	(1)%
Other Specialty (1)	70,009	86,432	(19)%
Total Specialty Products	$ 621,700	$ 633,150	(2)%
Established Products:			
PERCOCET®	$ 103,943	$ 103,788	— %
TESTOPEL®	38,727	43,636	(11)%
Other Established (2)	86,772	113,043	(23)%
Total Established Products	$ 229,442	$ 260,467	(12)%
Total Branded Pharmaceuticals (3)	$ 851,142	$ 893,617	(5)%

(1) Products included within Other Specialty include AVEED®, NASCOBAL® Nasal Spray and QWO®
(2) Products included within Other Established include, but are not limited to, EDEX®
(3) Individual products presented above represent the top two performing products in each product category for the year ended December 31, 2022 and/or any product having revenues in excess of $25 million during any completed quarterly period in 2022 or 2021

Specialty Products

Certain of our products that are physician administered, including XIAFLEX®, generally experienced decreased sales volumes during the COVID-19 pandemic due to reduced physician office activity and patient office visits because of the COVID-19 pandemic. While these products have generally been recovering since early 2020, they have at times continued to be impacted by COVID-19-related and, more recently, other market conditions for specialty product office-based procedures, including medical and administrative staff shortages in physicians' offices, reduced physician office activity and lower numbers of in-person patient office visits. The pandemic and other market conditions also created a high backlog of demand for non-elective urology procedures, which has in certain cases reduced the utilization of XIAFLEX® by healthcare providers. Additionally, we believe that concerns by healthcare providers regarding economic uncertainty have impacted purchasing patterns of XIAFLEX®. Changes in market conditions and certain other factors could result in revenue decreases or otherwise impact future periods, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

The increase in XIAFLEX® revenues in 2022 was primarily attributable to increased net price, partially offset by lower volumes. The decrease in volumes was primarily driven by continued challenging market conditions as further described above and the ongoing impact from a disruption experienced by our third-party specialty pharmacy provider during the third quarter of 2022. While we have since seen some recovery in volumes related to this disruption, volumes have not yet returned to pre-disruption levels.

The decrease in SUPPRELIN® LA revenues in 2022 was primarily attributable to decreased volumes, partially offset by increased net price.

The decrease in Other Specialty revenues in 2022 was primarily attributable to decreased NASCOBAL® Nasal Spray revenues, partially offset by increased AVEED® revenues.

Established Products

The decrease in TESTOPEL® revenues in 2022 was primarily attributable to decreased volumes.

The decrease in Other Established revenues in 2022 was primarily attributable to ongoing competitive pressures impacting this product portfolio and certain other factors.

Our Established Products portfolio is likely to continue to be affected by ongoing competitive pressures. This could result in revenue decreases or otherwise impact future periods, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Sterile Injectables. The following table displays the significant components of our Sterile Injectables revenues from external customers for the years ended December 31, 2022 and 2021 (dollars in thousands):

	2022	2021	% Change 2022 vs. 2021
VASOSTRICT®	$ 253,696	$ 901,735	(72)%
ADRENALIN®	114,304	124,630	(8)%
Other Sterile Injectables (1)	221,633	239,732	(8)%
Total Sterile Injectables (2)	$ 589,633	$ 1,266,097	(53)%

(1) Products included within Other Sterile Injectables include APLISOL®, ertapenem for injection and others
(2) Individual products presented above represent the top two performing products within the Sterile Injectables segment for the year ended December 31, 2022 and/or any product having revenues in excess of $25 million during any completed quarterly period in 2022 or 2021

The decrease in VASOSTRICT® revenues in 2022 was primarily driven by decreases to both net price and volumes, which were primarily attributable to the impact of generic competition as well as lower overall market demand as COVID-19-related hospital utilization levels declined. During the first quarter of 2022, multiple competitive generic alternatives to VASOSTRICT® were launched, beginning with a generic that was launched at risk and began shipping toward the end of January 2022. Since then, additional competitive alternatives entered the market, including authorized generics. These launches began to significantly impact both Endo's market share and product price toward the middle of the first quarter of 2022, and the effects of competition have since increased. Additionally, beginning late in the first quarter of 2022, COVID-19-related hospital utilization levels began to decline, resulting in significantly decreased market volumes for both branded and competing generic alternatives to VASOSTRICT®. In February 2022, we launched VASOSTRICT® in an RTU bottle, representing the first and only RTU formulation of the drug. The bottle formulation now represents a meaningful portion of the overall vasopressin market. Nevertheless, the factors described above could have a material adverse effect on our business, financial condition, results of operations and cash flows. For additional information, refer to Note 16. Commitments and Contingencies in the Consolidated Financial Statements included in Part IV, Item 15 of this report under the heading "Patent Matters."

The decrease in ADRENALIN® revenues in 2022 was primarily attributable to decreased net price and volumes.

The decrease in Other Sterile Injectables revenues in 2022 was primarily attributable to decreased price, partially offset by increased volumes.

Our Sterile Injectables segment is likely to continue to be affected by ongoing competitive pressures. This could result in revenue decreases or otherwise impact future periods, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Generic Pharmaceuticals. The increase in Generic Pharmaceuticals revenues in 2022 was primarily attributable to revenues from varenicline tablets (our generic version of Pfizer Inc.'s Chantix®), which launched in September 2021, partially offset by competitive pressures on certain generic products.

During the first quarter of 2023, a competitor launched an alternative generic version of varenicline tablets. This launch began to impact both Endo's market share and product price toward the middle of the first quarter of 2023, resulting in a decline in revenue for our Generic Pharmaceuticals segment. The effects of competition are likely to increase in future periods. Other products in our Generic Pharmaceuticals segment are also likely to continue to be affected by ongoing competitive pressures. These factors could result in revenue decreases or otherwise impact future periods, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

International Pharmaceuticals. The decrease in International Pharmaceuticals revenues in 2022 was primarily attributable to competitive pressures and the expiration of a product agreement. This segment is likely to continue to be affected by ongoing competitive pressures. This could result in revenue decreases or otherwise impact future periods, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Segment adjusted income from continuing operations before income tax. The following table displays our Segment adjusted income from continuing operations before income tax (the measure we use to evaluate segment performance) by reportable segment for the years ended December 31, 2022 and 2021 (dollars in thousands):

	2022	2021	% Change 2022 vs. 2021
Branded Pharmaceuticals	$ 366,554	$ 384,186	(5)%
Sterile Injectables	$ 349,424	$ 998,453	(65)%
Generic Pharmaceuticals	$ 336,133	$ 160,046	NM
International Pharmaceuticals	$ 19,920	$ 30,325	(34)%

NM indicates that the percentage change is not meaningful or is greater than 100%

Branded Pharmaceuticals. The decrease in Segment adjusted income from continuing operations before income tax in 2022 was primarily attributable to the gross margin effects of the decreased segment revenues further described above, as well as increased costs associated with our investment in consumer marketing efforts supporting XIAFLEX® and certain legal matters, partially offset by decreased costs associated with our commercial investment in QWO®.

Sterile Injectables. The decrease in Segment adjusted income from continuing operations before income tax in 2022 was primarily attributable to the gross margin effects of the decreased segment revenues further described above.

Generic Pharmaceuticals. The increase in Segment adjusted income from continuing operations before income tax in 2022 was primarily attributable to the gross margin effects of the increased segment revenues further described above, as well as the favorable changes in product mix, which primarily related to varenicline tablets.

International Pharmaceuticals. The decrease in Segment adjusted income from continuing operations before income tax in 2022 was primarily attributable to the gross margin effects of the decreased segment revenues further described above.

LIQUIDITY AND CAPITAL RESOURCES

On the Petition Date, the Debtors filed voluntary petitions for relief under the Bankruptcy Code, which constituted an event of default that accelerated our obligations under substantially all of our then-outstanding debt instruments. However, section 362 of the Bankruptcy Code stays creditors from taking any action to enforce the related financial obligations and creditors' rights of enforcement in respect of the debt instruments are subject to the applicable provisions of the Bankruptcy Code. Refer to Note 1. Description of Business, Note 2. Bankruptcy Proceedings and Note 15. Debt in the Consolidated Financial Statements included in Part IV, Item 15 of this report for further discussion.

Our principal source of liquidity is cash generated from operations. Cash and cash equivalents, which primarily consisted of bank deposits and money market accounts, totaled $1,018.9 million at December 31, 2022 compared to $1,507.2 million at December 31, 2021. Our principal liquidity requirements are primarily for working capital for operations, licenses, capital expenditures, mergers and acquisitions (including upfront and milestone payments to third parties), income taxes, litigation-related and other contingent liabilities, debt service payments (including adequate protection payments on our First Lien Debt Instruments (as defined below)) and other amounts related to our bankruptcy proceedings.

Our business is exposed to a variety of material risks as further described herein. For example, we may face decreased revenues as a result of COVID-19 and, to the extent COVID-19 has resulted in any increase to our Cash and cash equivalents, including as a result of any increase in revenues, such increase could be temporary. We may face unexpected costs in connection with our business operations, our ongoing and future legal proceedings, governmental investigations and other contingent liabilities (including potential costs related to settlements and judgments, as well as legal defense costs), our ongoing bankruptcy proceedings and the implementation of our COVID-19 related policies and procedures. On a longer-term basis, we may not be able to accurately predict the effect of certain developments on our sales and gross margins, such as the degree of market acceptance, patent protection and exclusivity of our products, pricing pressures (including those due to the impact of competition), the effectiveness of our sales and marketing efforts and the outcome of our current efforts to develop, receive approval for and successfully launch our product candidates. Furthermore, we may not be successful in implementing, or may face unexpected changes or expenses in connection with, our strategic direction, including the potential for opportunistic corporate development transactions. Additionally, as further discussed in Note 1. Description of Business in the Consolidated Financial Statements included in Part IV, Item 15 of this report, management has concluded that there is substantial doubt regarding our ability to continue as a going concern. Any of the above could have a material adverse effect on our business, financial condition, results of operations and cash flows and require us to seek additional sources of liquidity and capital resources as described below.

To the extent we are required or choose to seek third-party financing in the future, there can be no assurance that we would be able to obtain any such required financing on a timely basis or at all, particularly in light of our ongoing bankruptcy proceedings and the corresponding event of default on our existing debt instruments. Additionally, any future financing arrangements could include terms that are not commercially beneficial to us, which could further restrict our operations and exacerbate any impact on our results of operations and liquidity that may result from any of the factors described herein or other factors.

Refer to Note 21. Income Taxes in the Consolidated Financial Statements included in Part IV, Item 15 of this report for a discussion of our indefinite reinvestment assertion relating to undistributed earnings of certain of our subsidiaries.

Indebtedness. The Company and certain of its subsidiaries are party to the Credit Agreement (as defined below) governing the Credit Facilities (as defined below) and the indentures governing our various senior secured and senior unsecured notes. Refer to Note 2. Bankruptcy Proceedings and Note 15. Debt in the Consolidated Financial Statements included in Part IV, Item 15 of this report for additional information about our indebtedness, including information about amounts currently outstanding, maturities, interest rates, security, priority, certain recent debt financing transactions and the effects of bankruptcy-related proceedings and the corresponding event of default.

Working capital. The components of our working capital and our liquidity at December 31, 2022 and December 31, 2021 are below (dollars in thousands):

	December 31, 2022	December 31, 2021
Total current assets	$ 2,076,768	$ 2,714,586
Less: total current liabilities	689,627	1,629,962
Working capital	$ 1,387,141	$ 1,084,624
Current ratio (total current assets divided by total current liabilities)	3.0:1	1.7:1

Net working capital increased by $302.5 million from December 31, 2021 to December 31, 2022. During this period, working capital benefited from the favorable impacts to net current assets resulting from revenues and gross margins, which are further described above. These benefits were partially offset by, among other things, the following current period activity: (i) Capital expenditures, excluding capitalized interest, net of Proceeds from the U.S. Government Agreement, of $81.1 million; (ii) Acquired in-process research and development charges of $68.7 million; and (iii) certain expenses incurred in connection with our bankruptcy proceedings and certain restructuring and other cost reduction initiatives.

Our bankruptcy proceedings have also resulted in adjustments to the classification of certain assets and liabilities in our Consolidated Balance Sheets during 2022, which have resulted in significant changes to our working capital. For example, many liabilities previously included in current liabilities have been reclassified as Liabilities subject to compromise and are therefore no longer part of our working capital. The classification of our assets and liabilities in our Consolidated Balance Sheets may continue to change significantly during bankruptcy proceedings, which could result in material changes to our working capital in future periods. Refer to Note 2. Bankruptcy Proceedings and Note 15. Debt in the Consolidated Financial Statements included in Part IV, Item 15 of this report for additional information.

The following table summarizes our Consolidated Statements of Cash Flows for the years ended December 31, 2022 and 2021 (in thousands):

	2022	2021
Net cash flow provided by (used in):		
Operating activities	$ 269,193	$ 411,050
Investing activities	(133,147)	(59,544)
Financing activities	(513,873)	(105,481)
Effect of foreign exchange rate	(4,242)	285
Net (decrease) increase in cash, cash equivalents, restricted cash and restricted cash equivalents	$ (382,069)	$ 246,310

Operating activities. Net cash provided by operating activities represents the cash receipts and cash disbursements from all of our activities other than investing activities and financing activities. Changes in cash from operating activities reflect, among other things, the timing of cash collections from customers, payments to suppliers, MCOs, government agencies, collaborative partners and employees in the ordinary course of business, as well as the timing and amount of cash payments and/or receipts related to interest, litigation-related matters, restructurings, reorganization items, income taxes and certain other items.

The $141.9 million decrease in Net cash provided by operating activities in 2022 compared to the prior year period was primarily due to reduced VASOSTRICT® revenues, partially offset by decreased payments to settle a variety of liabilities resulting from payment delays and/or other reductions related to our contingency planning and bankruptcy proceedings. Additionally, as further discussed in Note 15. Debt in the Consolidated Financial Statements included in Part IV, Item 15 of this report, we are not currently making interest payments (which have historically been reflected as operating cash flows) on most of our debt instruments; we have instead begun making certain adequate protection payments related to our First Lien Debt Instruments, which are currently being reflected as financing cash flows.

It is possible that our operating cash flows could decline in the future as a result of, among other things, reductions to revenues and payments in future periods related to liabilities for which payment has been delayed as part of our contingency planning and bankruptcy proceedings. Additionally, it is possible that some or all of the adequate protection payments described above may later be recharacterized as interest expense depending upon certain developments in the Chapter 11 Cases, which could result adequate protection payments being reflected as operating cash flows in future periods, which could in turn lead to decreases to our operating cash flows that may be material.

Investing activities. The $73.6 million increase in Net cash used in investing activities in 2022 compared to the prior year period was primarily attributable to: (i) an increase in Acquisitions, including in-process research and development, net of cash and restricted cash acquired of $85.3 million and (ii) an increase in Capital expenditures, excluding capitalized interest of $21.8 million. The changes were partially offset by: (i) an increase in Proceeds from the U.S. Government Agreement of $18.6 million and (ii) an increase in Proceeds from sale of business and other assets, net of $11.1 million.

Financing activities. During 2022, Net cash used in financing activities primarily related to: (i) Adequate protection payments of $313.1 million; (ii) Repayments of notes of $180.3 million; and (iii) Repayments of term loans of $10.0 million.

During 2021, Net cash used in financing activities related primarily to: (i) the March 2021 Refinancing Transactions, including the payment of approximately $43.6 million of associated costs and fees; (ii) Repayments of revolving debt of $22.8 million; (iii) Repayments of term loans subsequent to the March 2021 Refinancing Transactions of $15.0 million; and (iv) Payments of tax withholding for restricted shares of $14.8 million.

R&D. As further described above under the heading “RESULTS OF OPERATIONS,” in recent years, we have incurred significant expenditures related to R&D. We expect to continue incur R&D expenditures related to the development and advancement of our current product pipeline and any additional product candidates we may add via license, acquisition or organically. There can be no assurance that the results of any ongoing or future nonclinical or clinical trials related to these projects will be successful, that additional trials will not be required, that any compound, product or indication under development will receive regulatory approval in a timely manner or at all or that such compound, product or indication could be successfully manufactured in accordance with local current good manufacturing practices or marketed successfully, or that we will have sufficient funds to develop or commercialize any of our products.

Manufacturing, supply and other service agreements. We contract with various third-party manufacturers, suppliers and service providers to supply our products, or materials used in the manufacturing of our products, and to provide additional services such as packaging, processing, labeling, warehousing, distribution and customer service support. Any interruption to the goods or services provided for by these and similar contracts could have a material adverse effect on our business, financial condition, results of operations and cash flows.

License, collaboration and asset acquisition agreements. We could become obligated to make certain contingent payments pursuant to our license, collaboration and asset acquisition agreements. Except for upfront payments, payments under these agreements generally become due and payable only upon the achievement of certain developmental, regulatory, commercial and/or other milestones. Due to the fact that it is uncertain whether and when certain of these milestones will be achieved, they have not been recorded in our Consolidated Balance Sheets. In addition, we may be required to make sales-based royalty or similar payments under certain arrangements.

Legal proceedings. We are subject to various patent challenges, product liability claims, government investigations and other legal proceedings in the ordinary course of business. Contingent accruals are recorded when we determine that a loss is both probable and reasonably estimable. Due to the fact that legal proceedings and other contingencies are inherently unpredictable, our assessments involve significant judgments regarding future events. For additional discussion of legal proceedings, see Note 16. Commitments and Contingencies in the Consolidated Financial Statements included in Part IV, Item 15 of this report.

Cash Requirements for Contractual and Other Obligations. As of December 31, 2022, we have various contractual and other obligations that we expect will require the use of cash in both the short-term and long-term. These include, without limitation, the following: (i) payments related to our debt, including principal and interest and/or adequate protection payments; (ii) lease payments; (iii) obligations related to license and collaboration agreements; (iv) commitments for capital expenditures; (v) other purchase obligations, which represent enforceable and legally binding obligations for purchases of goods and services, including minimum inventory contracts, that specify all significant terms, including fixed or minimum quantities to be purchased, fixed, minimum or variable price provisions and timing; and (vi) contractual payments for certain legal liability settlements.

Refer to Note 9. Leases, Note 12. License, Collaboration and Asset Acquisition Agreements, Note 15. Debt and Note 16. Commitments and Contingencies in the Consolidated Financial Statements included in Part IV, Item 15 of this report for additional information about these obligations including, to the extent material, quantitative information about the related cash requirements.

Information about our unrecognized income tax positions is included in Note 21. Income Taxes in the Consolidated Financial Statements included in Part IV, Item 15 of this report. Due to the nature and timing of the ultimate outcome of these unrecognized income tax positions, we cannot make a reliable estimate of the amount and period of related future payments, if any.

The Chapter 11 Cases have affected and are likely to continue to affect certain of the obligations described above, as further discussed herein. As the Chapter 11 Cases progress, certain of our contractual arrangements could be amended or rejected, which could result in changes to our cash requirements for such obligations.

Additionally, we have made significant cash payments to date as a direct result of our ongoing bankruptcy proceedings, including payments for related professional fees. We expect to continue to incur significant expenditures in the future as a result of our bankruptcy proceedings and certain related transactions. It is possible that our expenditures will increase over time, particularly if we incur certain associated success-related and/or other contingent fees, which could be significant. In addition, the longer the Chapter 11 Cases continue, the higher our expenditures for these matters could be.

For additional discussion of our bankruptcy proceedings, refer to Note 2. Bankruptcy Proceedings in the Consolidated Financial Statements included in Part IV, Item 15 of this report.

Fluctuations. Our quarterly results have fluctuated in the past and may continue to fluctuate. These fluctuations may be due to the business and financial statement effects of, among other things, new product launches by us or our competitors; market acceptance of our products; purchasing patterns of our customers; changes in pricing; changing inflation and interest rates; changes in the availability of our products; litigation-related and other contingencies; mergers, acquisitions, divestitures and other related activity; restructurings and other cost-reduction initiatives; bankruptcy proceedings and strategic review initiatives; financing activities; COVID-19; acquired in-process research and development charges; asset impairment charges; share-based and other long-term incentive compensation; and changes in the fair value of financial instruments. Additionally, a substantial portion of our total revenues are through three wholesale distributors who in turn supply our products to pharmacies, hospitals and physicians. Accordingly, we are potentially subject to a concentration of credit risk with respect to our trade receivables.

Inflation. Materials, equipment and labor shortages, shipping, logistics and other delays and other supply chain and manufacturing disruptions, whether due to the evolving effects of the COVID-19 pandemic or otherwise, continue to make it more difficult and costly for us to obtain raw materials, supplies or services from third parties, to manufacture our own products and to pursue clinical development activities. Economic or political instability or disruptions, such as the conflict in Ukraine, could negatively affect our supply chain or increase our costs. While we do not believe that inflation had a material adverse effect on our financial statements for the periods presented, if these types of events or disruptions continue to occur, they could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Off-balance sheet arrangements. We have no off-balance sheet arrangements.

Item 7A. ***Quantitative and Qualitative Disclosures About Market Risk***

Market risk is the potential loss arising from adverse changes in the financial markets, including interest rates and foreign currency exchange rates.

Interest Rate Risk

Our exposure to interest rate risk relates primarily to our variable-rate indebtedness associated with our Credit Facilities. Borrowings under the Credit Facilities may from time to time require payments calculated using variable rates, in certain cases subject to a floor. At December 31, 2022 and December 31, 2021, a hypothetical 1% increase in the applicable rate over any applicable floor would have resulted in the incurrence of $22.5 million and $22.6 million, respectively, of incremental payments (representing the annual rate of incurrence) related to our variable-rate debt borrowings.

As of December 31, 2022 and December 31, 2021, we had no other assets or liabilities with significant interest rate sensitivity.

Foreign Currency Exchange Rate Risk

We operate and transact business in various foreign countries and are therefore subject to risks associated with foreign currency exchange rate fluctuations. The Company manages this foreign currency risk, in part, through operational means including managing foreign currency revenues in relation to same-currency costs and foreign currency assets in relation to same-currency liabilities. The Company is also exposed to potential earnings effects from intercompany foreign currency assets and liabilities that arise from normal trade receivables and payables and other intercompany loans. Additionally, certain of the Company's subsidiaries maintain their books of record in currencies other than their respective functional currencies. These subsidiaries' financial statements are remeasured into their respective functional currencies. Such remeasurement adjustments could have a material adverse effect on our business, financial condition, results of operations and cash flows.

The assets and liabilities of certain of our international subsidiaries are also translated to U.S. dollars at period-end exchange rates. Translation adjustments arising from the use of differing exchange rates are included in Accumulated other comprehensive loss. Gains and losses on foreign currency transactions and short-term intercompany receivables from foreign subsidiaries are included in Other income, net in the Consolidated Statements of Operations. Refer to Note 20. Other Income, Net in the Consolidated Financial Statements included in Part IV, Item 15 of this report for the amounts of Foreign currency (gain) loss, net.

Based on the Company's significant foreign currency denominated intercompany loans, we separately considered the hypothetical impact of a 10% change in the underlying currencies of our foreign currency denominated intercompany loans, relative to the U.S. dollar, at December 31, 2022 and December 31, 2021. A 10% change at December 31, 2022 and December 31, 2021 would have resulted in approximately $11 million in incremental foreign currency losses on such dates.

Item 8. ***Financial Statements and Supplementary Data***

The information required by this item is contained in the financial statements set forth in Item 15. under the caption "Consolidated Financial Statements" as part of this Annual Report on Form 10-K.

Item 9. ***Changes in and Disagreements with Accountants on Accounting and Financial Disclosure***

Not applicable.

Item 9A. ***Controls and Procedures***

(a) Evaluation of Disclosure Controls and Procedures

The Company's management, with the participation of the Company's Chief Executive Officer and Principal Financial Officer, has evaluated the effectiveness of the Company's disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) of the Exchange Act, as of December 31, 2022. Based on that evaluation, the Company's Chief Executive Officer and Principal Financial Officer concluded that the Company's disclosure controls and procedures were effective as of December 31, 2022.

(b) Management's Report on Internal Control over Financial Reporting

The report of management of the Company regarding internal control over financial reporting is set forth in Item 15. of this Annual Report on Form 10-K under the caption "MANAGEMENT'S REPORT ON INTERNAL CONTROL OVER FINANCIAL REPORTING" and incorporated herein by reference.

(c) Attestation Report of Independent Registered Public Accounting Firm

The attestation report of the Company's independent registered public accounting firm regarding internal control over financial reporting is set forth in Item 15. of this Annual Report on Form 10-K under the caption "REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM" and incorporated herein by reference.

(d) Changes in Internal Control over Financial Reporting

There have been no changes in the Company's internal control over financial reporting during the fiscal quarter ended December 31, 2022 that have materially affected, or are reasonably likely to materially affect, the Company's internal control over financial reporting.

Item 9B. ***Other Information***

None.

Item 9C. ***Disclosure Regarding Foreign Jurisdictions that Prevent Inspections***

None.

PART III

Item 10. ***Directors, Executive Officers and Corporate Governance***

The information required under this item will be provided in an amendment filed on Form 10-K/A.

Item 11. ***Executive Compensation***

The information required under this item will be provided in an amendment filed on Form 10-K/A.

Item 12. ***Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters***

The information required under this item will be provided in an amendment filed on Form 10-K/A.

Item 13. ***Certain Relationships and Related Transactions, and Director Independence***

The information required under this item will be provided in an amendment filed on Form 10-K/A.

Item 14. ***Principal Accountant Fees and Services***

The information required under this item will be provided in an amendment filed on Form 10-K/A.

PART IV

Item 15. ***Exhibit and Financial Statement Schedules***

(a) The following documents are filed as part of this report:

1. *The Consolidated Financial Statements*

Management's Report on Internal Control Over Financial Reporting
Report of Independent Registered Public Accounting Firm (PCAOB ID 238)
Consolidated Balance Sheets as of December 31, 2022 and 2021
Consolidated Statements of Operations for the years ended December 31, 2022, 2021 and 2020
Consolidated Statements of Comprehensive (Loss) Income for the years ended December 31, 2022, 2021 and 2020
Consolidated Statements of Shareholders' Deficit for the years ended December 31, 2022, 2021 and 2020
Consolidated Statements of Cash Flows for the years ended December 31, 2022, 2021 and 2020
Notes to Consolidated Financial Statements

2. *Financial Statement Schedules*

SCHEDULE II—VALUATION AND QUALIFYING ACCOUNTS
(in thousands)

	Balance at Beginning of Period	Additions, Costs and Expenses	Deductions, Write-offs	Other (1)	Balance at End of Period
Valuation Allowance For Deferred Tax Assets:					
Year Ended December 31, 2020	$ 9,828,959	$ 150,500	$ (316,474)	$ 5,571	$ 9,668,556
Year Ended December 31, 2021	$ 9,668,556	$ 504,499	$ (9)	$ (3,752)	$ 10,169,294
Year Ended December 31, 2022	$ 10,169,294	$ 273,538	$ (46)	$ (6,367)	$ 10,436,419

(1) Represents the remeasurement of net deferred tax assets due to changes in statutory tax rates

All other financial statement schedules have been omitted because they are not applicable or the required information is included in the Consolidated Financial Statements or the Notes thereto.

3. *Exhibits*

		Incorporated by Reference from:		
Number	**Description**	**File Number**	**Filing Type**	**Filing Date**
2.1†	Agreement and Plan of Merger, dated as of October 19, 2020, by and among BioSpecifics Technologies Corp., Endo International plc, and Beta Acquisition Corp.	001-36326	Current Report on Form 8-K	October 19, 2020
3.1	Certificate of Incorporation on re-registration as a public limited company of Endo International plc	001-36326	Current Report on Form 8-K12B	February 28, 2014
3.2	Memorandum and Articles of Association of Endo International plc, dated as of October 31, 2013 and as amended as of June 8, 2017	001-36326	Quarterly Report on Form 10-Q	August 8, 2017
4.1	Specimen Share Certificate of Endo International plc	333-194253	Form S-8	February 28, 2014
4.2	Indenture, dated January 27, 2015, among Endo Designated Activity Company (formerly, Endo Limited), Endo Finance LLC, Endo Finco Inc., the guarantors named therein and Wells Fargo Bank, National Association, as trustee, relating to the 6.00% Senior Notes due 2025 (including Form of 6.00% Senior Notes due 2025 and Form of Supplemental Indenture relating to the 6.00% Senior Notes due 2025)	001-36326	Current Report on Form 8-K	January 27, 2015
4.2.1	Supplemental Indenture, dated March 27, 2015, among Endo Designated Activity Company (formerly, Endo Limited), Endo Finance LLC, Endo Finco Inc., the guarantors named therein and Wells Fargo Bank, National Association, as trustee, to the Indenture, dated January 27, 2015	001-36326	Annual Report on Form 10-K	February 29, 2016

		Incorporated by Reference from:		
Number	Description	File Number	Filing Type	Filing Date
4.2.2	Supplemental Indenture, dated as of May 28, 2020, among Endo Designated Activity Company, Endo Finance LLC, Endo Finco Inc., the guarantors named therein and Wells Fargo Bank, National Association, as trustee, to the Indenture, dated as of January 27, 2015, among Endo Designated Activity Company, Endo Finance LLC, Endo Finco Inc., the guarantors named therein and Wells Fargo Bank, National Association, as trustee, relating to the 6.000% Senior Notes due 2025	001-36326	Current Report on Form 8-K	June 16, 2020
4.3	Registration Rights Agreement, dated January 27, 2015, by and among Endo Designated Activity Company (formerly, Endo Limited), Endo Finance LLC, Endo Finco Inc., the guarantors named therein and RBC Capital Markets, LLC and Citigroup Global Markets Inc., relating to the 6.00% Senior Notes due 2025 (including Form of Counterpart to the Registration Rights Agreement relating to the 6.00% Senior Notes due 2025)	001-36326	Current Report on Form 8-K	January 27, 2015
4.4	Indenture, dated July 9, 2015, among Endo Designated Activity Company (formerly, Endo Limited), Endo Finance LLC, Endo Finco Inc., the guarantors named therein and Wells Fargo Bank, National Association, as trustee, relating to the 6.000% Senior Notes due 2023 (including Form of 6.000% Notes due 2023 and Form of Supplemental Indenture relating to the 6.000% Notes due 2023)	001-36326	Current Report on Form 8-K	July 9, 2015
4.4.1	Supplemental Indenture, dated as of May 28, 2020, among Endo Designated Activity Company, Endo Finance LLC, Endo Finco Inc., the guarantors named therein and Wells Fargo Bank, National Association, as trustee, to the Indenture, dated as of July 9, 2015, among Endo Designated Activity Company, Endo Finance LLC, Endo Finco Inc., the guarantors named therein and Wells Fargo Bank, National Association, as trustee, relating to the 6.000% Senior Notes due 2023	001-36326	Current Report on Form 8-K	June 16, 2020
4.5	Indenture, dated as of March 28, 2019, among Par Pharmaceutical, Inc., the guarantors named therein and Wells Fargo Bank, National Association, as trustee, relating to the 7.500% Senior Secured Notes due 2027 (including Form of 7.500% Senior Secured Notes due 2027)	001-36326	Current Report on Form 8-K	March 28, 2019
4.5.1	First Supplemental Indenture, dated as of June 16, 2020, among Par Pharmaceutical, Inc., the guarantors named therein and Wells Fargo Bank, National Association, as trustee, to the Indenture, dated as of March 28, 2019, among Par Pharmaceutical, Inc., the guarantors named therein and Wells Fargo Bank, National Association, as trustee, relating to the 7.500% Senior Secured Notes due 2027	001-36326	Current Report on Form 8-K	June 16, 2020
4.6	Indenture, dated as of June 16, 2020, among Endo Designated Activity Company, Endo Finance LLC, Endo Finco Inc., the guarantors named therein and Wells Fargo Bank, National Association, as trustee, relating to the 9.500% Senior Secured Second Lien Notes due 2027 (including Form of 9.500% Senior Secured Second Lien Notes due 2027)	001-36326	Current Report on Form 8-K	June 16, 2020
4.7	Indenture, dated as of June 16, 2020, among Endo Designated Activity Company, Endo Finance LLC, Endo Finco Inc., the guarantors named therein and Wells Fargo Bank, National Association, as trustee, relating to the 6.000% Senior Notes due 2028 (including Form of 6.000% Senior Notes due 2028)	001-36326	Current Report on Form 8-K	June 16, 2020
4.8	Indenture, dated as of March 25, 2021, among Endo Luxembourg Finance Company I S.à r.l., Endo U.S. Inc., the guarantors named therein and Wells Fargo Bank, National Association, as trustee, relating to the 6.125% Senior Secured Notes due 2029 (including Form of 6.125% Senior Secured Notes due 2029)	001-36326	Current Report on Form 8-K	March 25, 2021
10.1	Amended and Restated Executive Deferred Compensation Plan	001-36326	Quarterly Report on Form 10-Q	August 8, 2018
10.2	Amended and Restated 401(k) Restoration Plan	001-15989	Annual Report on Form 10-K	March 1, 2013

		Incorporated by Reference from:		
Number	Description	File Number	Filing Type	Filing Date
10.3	Directors Deferred Compensation Plan	001-15989	Annual Report on Form 10-K	March 1, 2013
10.4	Endo International plc Amended and Restated Employee Stock Purchase Plan	333-194253	Form S-8	February 28, 2014
10.5	Amendment and Restatement Agreement, dated as of March 25, 2021, by and among Endo International plc, Endo Luxembourg Finance Company I S.à r.l., Endo LLC, the lenders and other parties party thereto and JPMorgan Chase Bank, N.A. as administrative agent, issuing bank and swingline lender, which amends and restates the Credit Agreement, dated as of April 27, 2017	001-36326	Current Report on Form 8-K	March 25, 2021
10.6	Collateral Trust Agreement, dated as of April 27, 2017, by and among Endo International plc, certain subsidiaries of Endo International plc as borrowers, Par Pharmaceutical, Inc., certain other grantors party thereto, JPMorgan Chase Bank, N.A. as administrative agent, Wells Fargo Bank, National Association, as trustee, and Wilmington Trust, National Association, as collateral trustee	001-36326	Current Report on Form 8-K	June 16, 2020
10.7	Second Lien Collateral Trust Agreement, dated as of June 16, 2020, by and among Endo International plc, certain subsidiaries of Endo International plc as borrowers, Endo Designated Activity Company, Endo Finance LLC, Endo Finco Inc., certain other grantors party thereto, JPMorgan Chase Bank, N.A. as administrative agent, Wells Fargo Bank, National Association, as trustee, and Wilmington Trust, National Association, as collateral trustee	001-36326	Current Report on Form 8-K	June 16, 2020
10.8	Intercreditor Agreement, dated as of June 16, 2020, by and among Wilmington Trust, National Association, as first priority representative, Wilmington Trust, National Association, as second priority representative, and certain grantors party thereto	001-36326	Current Report on Form 8-K	June 16, 2020
10.9*	Supply Agreement, dated June 26, 2008, between Auxilium and Hollister-Stier Laboratories LLC	000-50855	Quarterly Report on Form 10-Q	August 8, 2008
10.10	Endo International plc Amended and Restated 2015 Stock Incentive Plan	001-36326	Current Report on Form 8-K	June 11, 2020
10.11	Form of Stock Option Agreement under the Endo International plc Amended and Restated 2015 Stock Incentive Plan	001-36326	Quarterly Report on Form 10-Q	November 8, 2018
10.12	Form of Stock Award Agreement under the Endo International plc Amended and Restated 2015 Stock Incentive Plan	001-36326	Quarterly Report on Form 10-Q	May 7, 2021
10.13	Form of Performance Award Agreement under the Endo International plc Amended and Restated 2015 Stock Incentive Plan	001-36326	Quarterly Report on Form 10-Q	May 7, 2021
10.14	Form of Long-Term Cash Award Agreement under the Endo International plc Amended and Restated 2015 Stock Incentive Plan	001-36326	Quarterly Report on Form 10-Q	May 7, 2021
10.15	Form of Long-Term Cash Incentive Award Agreement under the Amended and Restated 2015 Stock Incentive Plan	001-36326	Quarterly Report on Form 10-Q	August 8, 2018
10.16	Form of Indemnification Agreement with Endo Health Solutions Inc.	001-36326	Annual Report on Form 10-K	February 29, 2016
10.17	Form of Indemnification Agreement with Endo International plc	001-36326	Quarterly Report on Form 10-Q	May 6, 2016
10.18	Executive Employment Agreement between Endo Health Solutions Inc. and Blaise Coleman, dated February 19, 2020 and effective March 6, 2020	001-36326	Annual Report on Form 10-K	February 26, 2020
10.19	Executive Employment Agreement between Endo Health Solutions Inc. and Patrick Barry, effective April 26, 2020	001-36326	Quarterly Report on Form 10-Q	May 7, 2020
10.20	Executive Employment Agreement between Endo Health Solutions Inc. and Mark T. Bradley, dated February 19, 2020 and effective March 6, 2020	001-36326	Annual Report on Form 10-K	February 26, 2020

Number	Description	Incorporated by Reference from: File Number	Filing Type	Filing Date
10.21	Executive Employment Agreement between Endo Health Solutions Inc. and Matthew Maletta, effective February 13, 2021	001-36326	Quarterly Report on Form 10-Q	November 6, 2020
10.22	Amendment, dated as of August 13, 2022, to Executive Employment Agreement between Endo Health Solutions Inc. and Blaise Coleman, effective March 6, 2020	001-36326	Quarterly Report on Form 10-Q	November 9, 2022
10.23	Amendment, dated as of August 13, 2022, to Executive Employment Agreement between Endo Health Solutions Inc. and Patrick Barry, effective April 26, 2020	001-36326	Quarterly Report on Form 10-Q	November 9, 2022
10.24	Amendment, dated as of August 13, 2022, to Executive Employment Agreement between Endo Health Solutions Inc. and Mark T. Bradley, effective March 6, 2020	001-36326	Quarterly Report on Form 10-Q	November 9, 2022
10.25	Amendment, dated as of August 13, 2022, to Executive Employment Agreement between Endo Health Solutions Inc. and Matthew Maletta, effective February 13, 2021	001-36326	Quarterly Report on Form 10-Q	November 9, 2022
10.26	Retention Agreement between Endo and Blaise Coleman, dated November 1, 2021	001-36326	Annual Report on Form 10-K	March 1, 2022
10.27	Retention Agreement between Endo and Mark T. Bradley, dated November 1, 2021	001-36326	Annual Report on Form 10-K	March 1, 2022
10.28	Retention Agreement between Endo and Matthew J. Maletta, dated November 1, 2021	001-36326	Annual Report on Form 10-K	March 1, 2022
10.29	Retention Agreement between Endo and Patrick Barry, dated November 1, 2021	001-36326	Annual Report on Form 10-K	March 1, 2022
10.30	Retention Agreement between Endo and Blaise Coleman, dated August 11, 2022	001-36326	Quarterly Report on Form 10-Q	November 9, 2022
10.31	Retention Agreement between Endo and Mark T. Bradley, dated August 11, 2022	001-36326	Quarterly Report on Form 10-Q	November 9, 2022
10.32	Retention Agreement between Endo and Matthew J. Maletta, dated August 11, 2022	001-36326	Quarterly Report on Form 10-Q	November 9, 2022
10.33	Retention Agreement between Endo and Patrick Barry, dated August 11, 2022	001-36326	Quarterly Report on Form 10-Q	November 9, 2022
10.34	Restructuring Support Agreement, dated August 16, 2022, by and among the Debtors and the members of the Ad Hoc First Lien Group	001-36326	Current Report on Form 8-K	August 17, 2022
21.1	Subsidiaries of the Registrant	Not applicable; filed herewith		
24.1	Power of Attorney	Not applicable; filed herewith		
31.1	Certification of the President and Chief Executive Officer of Endo pursuant to Section 302 of the Sarbanes-Oxley Act of 2002	Not applicable; filed herewith		
31.2	Certification of the Chief Financial Officer of Endo pursuant to Section 302 of the Sarbanes-Oxley Act of 2002	Not applicable; filed herewith		
32.1	Certification of the President and Chief Executive Officer of Endo pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002	Not applicable; furnished herewith		
32.2	Certification of the Chief Financial Officer of Endo pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002	Not applicable; furnished herewith		
101.INS	iXBRL Instance Document - the instance document does not appear in the interactive data file because its XBRL tags are embedded within the inline XBRL document.	Not applicable; submitted herewith		
101.SCH	iXBRL Taxonomy Extension Schema Document	Not applicable; submitted herewith		
101.CAL	iXBRL Taxonomy Extension Calculation Linkbase Document	Not applicable; submitted herewith		
101.DEF	iXBRL Taxonomy Extension Definition Linkbase Document	Not applicable; submitted herewith		
101.LAB	iXBRL Taxonomy Extension Label Linkbase Document	Not applicable; submitted herewith		
101.PRE	iXBRL Taxonomy Extension Presentation Linkbase Document	Not applicable; submitted herewith		

Number	Description	Incorporated by Reference from: File Number	Filing Type	Filing Date
104	Cover Page Interactive Data File, formatted in iXBRL and contained in Exhibit 101	Not applicable; submitted herewith		

* Confidential portions of this exhibit (indicated by asterisks) have been redacted and filed separately with the Securities and Exchange Commission pursuant to a confidential treatment request in accordance with Rule 24b-2 of the Exchange Act.

† Schedules and exhibits have been omitted pursuant to Item 601(a)(5) of Regulation S-K.

Item 16. ***Form 10-K Summary***

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

ENDO INTERNATIONAL PLC
(Registrant)

/S/ BLAISE COLEMAN
Name: **Blaise Coleman**
Title: **President and Chief Executive Officer**
(Principal Executive Officer)

Date: March 6, 2023

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

	Signature	Title	Date
	/S/ BLAISE COLEMAN Blaise Coleman	Director, President and Chief Executive Officer (Principal Executive Officer)	March 6, 2023
	/S/ MARK T. BRADLEY Mark T. Bradley	Executive Vice President, Chief Financial Officer (Principal Financial Officer)	March 6, 2023
	/S/ FRANK B. RACITI Frank B. Raciti	Vice President, Controller, Chief Accounting Officer (Principal Accounting Officer)	March 6, 2023
	* Mark G. Barberio	Chairman and Director	March 6, 2023
	* Jennifer M. Chao	Director	March 6, 2023
	* Shane M. Cooke	Director	March 6, 2023
	* Nancy J. Hutson, Ph.D.	Director	March 6, 2023
	* Michael Hyatt	Director	March 6, 2023
	* William P. Montague	Director	March 6, 2023
	* M. Christine Smith, Ph.D.	Director	March 6, 2023
*By:	/S/ MATTHEW J. MALETTA Matthew J. Maletta	Attorney-in-fact pursuant to a Power of Attorney filed with this Report as Exhibit 24.1	March 6, 2023

INDEX TO FINANCIAL STATEMENTS

MANAGEMENT'S REPORT ON INTERNAL CONTROL OVER FINANCIAL REPORTING

The management of Endo International plc is responsible for establishing and maintaining adequate internal control over financial reporting as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act, as amended. Endo International plc's internal control over financial reporting was designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Endo International plc's management assessed the effectiveness of the Company's internal control over financial reporting as of December 31, 2022. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in *Internal Control-Integrated Framework (2013)*. Based on management's assessment, as of December 31, 2022, the Company's internal control over financial reporting is effective based on those criteria.

Endo International plc's independent registered public accounting firm has issued its report on the effectiveness of the Company's internal control over financial reporting as of December 31, 2022. This report appears on page F-3.

/S/ BLAISE COLEMAN

Blaise Coleman
President and Chief Executive Officer
(Principal Executive Officer)

/S/ MARK T. BRADLEY

Mark T. Bradley
Executive Vice President, Chief Financial Officer
(Principal Financial Officer)

March 6, 2023

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Board of Directors and Shareholders of Endo International plc

Opinions on the Financial Statements and Internal Control over Financial Reporting

We have audited the accompanying consolidated balance sheets of Endo International plc (Debtor-in-Possession) and its subsidiaries (the "Company") as of December 31, 2022 and 2021, and the related consolidated statements of operations, of comprehensive (loss) income, of shareholders' deficit and of cash flows for each of the three years in the period ended December 31, 2022, including the related notes and schedule of valuation and qualifying accounts for each of the three years in the period ended December 31, 2022 appearing under Item 15(a)(2) (collectively referred to as the "consolidated financial statements"). We also have audited the Company's internal control over financial reporting as of December 31, 2022, based on criteria established in *Internal Control - Integrated Framework* (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO).

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of the Company as of December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2022 in conformity with accounting principles generally accepted in the United States of America. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2022, based on criteria established in *Internal Control - Integrated Framework* (2013) issued by the COSO.

Substantial Doubt about the Company's Ability to Continue as a Going Concern

The accompanying consolidated financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Notes 1 and 2 to the consolidated financial statements, the Company, together with certain of its direct and indirect subsidiaries, filed voluntary petitions for relief under the Bankruptcy Code, which raises substantial doubt about its ability to continue as a going concern. Management's plans in regard to this matter are also described in Notes 1 and 2. The consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty. This matter is also discussed below as a critical audit matter.

Basis for Opinions

The Company's management is responsible for these consolidated financial statements, for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying Management's Report on Internal Control Over Financial Reporting. Our responsibility is to express opinions on the Company's consolidated financial statements and on the Company's internal control over financial reporting based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud, and whether effective internal control over financial reporting was maintained in all material respects.

Our audits of the consolidated financial statements included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide a reasonable basis for our opinions.

Definition and Limitations of Internal Control over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Critical Audit Matters

The critical audit matters communicated below are matters arising from the current period audit of the consolidated financial statements that were communicated or required to be communicated to the audit committee and that (i) relate to accounts or disclosures that are material to the consolidated financial statements and (ii) involved our especially challenging, subjective, or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matters below, providing separate opinions on the critical audit matters or on the accounts or disclosures to which they relate.

Sales Deduction Reserves

As described in Note 3 to the consolidated financial statements, the amount of revenue recognized by the Company is equal to the fixed amount of the transaction price, adjusted for management's estimates of a number of significant variable components including, but not limited to, estimates for chargebacks, rebates, sales incentives and allowances, DSA and other fees for services, returns and allowances, which management collectively refer to as sales deductions. As of December 31, 2022, reserves for sales deductions totaled $600.2 million. These amounts relate primarily to management's estimates of unsettled obligations for returns and allowances, rebates and chargebacks. The most significant sales deduction reserves relate to returns, wholesaler chargebacks and rebates for the Sterile Injectables and Generic Pharmaceuticals segments. Management estimates the reserves for sales deductions based on factors such as direct and indirect customers' buying patterns and the estimated resulting contractual deduction rates, historical experience, specific known market events and estimated future trends, current contractual and statutory requirements, industry data, estimated customer inventory levels, current contract sales terms with direct and indirect customers and other competitive factors.

The principal considerations for our determination that performing procedures relating to reserves for sales deductions is a critical audit matter are the significant judgment by management in developing these reserves, which in turn led to a high degree of auditor judgment, subjectivity, and effort in performing procedures and evaluating the reserves, as the reserves are based on direct and indirect customers' buying patterns and the estimated resulting contractual deduction rates, historical experience, estimated future trends, estimated customer inventory levels and current contract sales terms with direct and indirect customers.

Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming our overall opinion on the consolidated financial statements. These procedures included testing the effectiveness of controls relating to sales deductions, including the Company's controls over the assumptions used to estimate the corresponding reserves for sales deductions. These procedures also included, among others, (i) developing an independent estimate of the reserves for sales deductions utilizing direct and indirect customers' buying patterns and the estimated resulting contractual deduction rates, historical experience, estimated future trends, estimated customer inventory levels and current contract sales terms with direct and indirect customers, (ii) comparing the independent estimates to the sales deduction reserves recorded by management, (iii) evaluating management's estimates in previous years by comparing historical reserves to rebate payments and credits processed in subsequent periods, and (iv) testing actual payments made and amounts credited to both direct and indirect customers to evaluate whether the payments and credits were made in accordance with the contractual and mandated terms of the Company's rebate programs and returns policy.

Goodwill Impairment Assessments - Sterile Injectables Reporting Unit

As described in Notes 3 and 11 to the consolidated financial statements, the Company's goodwill balance for the Sterile Injectables reporting unit was $523.2 million as of December 31, 2022. An impairment assessment is conducted as of October 1, or more frequently whenever events or changes in circumstances indicate that the asset might be impaired. Management performs the goodwill impairment test by estimating the fair value of the reporting units using an income approach that utilizes a discounted cash flow model or, where appropriate, a market approach. The discounted cash flow models are dependent upon management's estimates of future cash flows and other factors including estimates of (i) future operating performance, including future sales, long-term growth rates, gross margins, operating expenses, discount rate and the probability of achieving the estimated cash flows and (ii) future economic conditions. As a result of impairment tests performed during the second and third quarters, the Company recognized goodwill impairment charges of $1,845.0 million during the year ended December 31, 2022.

The principal considerations for our determination that performing procedures relating to the goodwill impairment assessments for the Sterile Injectables reporting unit is a critical audit matter are the significant judgment by management when developing the fair value estimate of the reporting unit, which in turn led to a high degree of auditor judgment, subjectivity and effort in performing procedures and evaluating management's cash flows and significant assumptions related to future sales, long-term growth rates, gross margins, operating expenses, discount rates and the probability of achieving the estimated cash flows and future economic conditions. In addition, the audit effort involved the use of professionals with specialized skill and knowledge.

Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming our overall opinion on the consolidated financial statements. These procedures included testing the effectiveness of controls relating to management's goodwill impairment assessments, including controls over the identification of triggering events and valuation of the Sterile Injectables reporting unit. These procedures also included, among others, testing management's process for developing the fair value estimate of the Sterile Injectables reporting unit. Testing management's process included evaluating the appropriateness of the discounted cash flow models related to cash flow projections, testing the completeness and accuracy of underlying data used in the models, evaluating the reasonableness of the significant assumptions used by management related to future sales, long-term growth rates, gross margins, operating expenses, discount rates and the probability of achieving the estimated cash flows and future economic conditions, and testing the assignment of assets and liabilities to the Sterile Injectables reporting unit. Evaluating management's assumptions related to future sales, long-term growth rates, gross margins, operating expenses, discount rates and the probability of achieving the estimated cash flows and future economic conditions involved evaluating whether the assumptions used were reasonable considering (i) historical performance of the reporting unit, (ii) industry and economic forecasts and (iii) whether the assumptions were consistent with evidence obtained in other areas of the audit. Professionals with specialized skill and knowledge were used to assist in evaluating the appropriateness of the Company's discounted cash flow models and evaluating the reasonableness of the discount rates.

Bankruptcy Proceedings

As described above and in Notes 2 and 16 to the consolidated financial statements, the Company initiated bankruptcy proceedings during the third quarter of 2022. As disclosed by management, on August 16, 2022, Endo International plc, together with certain of its direct and indirect subsidiaries (the Debtors), filed voluntary petitions for relief under chapter 11 of title 11 of the United States Code (the Bankruptcy Code). As a result of the bankruptcy proceedings, management has applied generally accepted accounting principles applicable to reorganizations in preparing the consolidated financial statements. These accounting principles require that, for periods including and after the filing of a chapter 11 petition, the consolidated financial statements distinguish transactions and events that are directly associated with the reorganization from the ongoing operations of the business. For periods beginning with the third quarter of 2022, pre-petition unsecured and undersecured claims related to the Debtors that may be impacted by the bankruptcy reorganization process in the amount of $9,168.8 million have been classified as liabilities subject to compromise in the consolidated balance sheet as of December 31, 2022. Additionally, certain expenses, gains and losses resulting from and recognized during the bankruptcy proceedings in the amount of $203.0 million are recorded in reorganization items, net in the consolidated statements of operations for the year ended December 31, 2022. In connection with the Restructuring Support Agreement the Company entered into on August 16, 2022, among other things, one or more entities formed in a manner acceptable to an ad hoc group of certain creditors (the Purchaser) will serve as stalking horse bidder as the Company seeks to sell all or substantially all of its assets in a sale pursuant to section 363 of the Bankruptcy Code. The Purchaser's bid, along with certain resolutions reached in principle announced by the Debtors on March 3, 2023, provides for the establishment by the Purchaser of voluntary opioid trusts for the benefit of certain public, tribal and private opioid claimants in exchange for certain releases to be provided to (among others) the Purchaser and Endo International plc, its subsidiaries and affiliated entities and persons. The trusts would distribute up to a total of $584 million to eligible claimants that opt into the trust agreements by specified participation deadlines. Although the proposed voluntary opioid trusts would be funded by the Purchaser, and not by the Company or any of its subsidiaries, management believes the proposed funding amount represents the best estimate of liability relating to the contingencies associated with various opioid claims against the Company and its subsidiaries. As a result, approximately $453 million in charges were recorded during the year ended December 31, 2022 to adjust the Company's aggregate opioid liability accrual to approximately $584 million as of December 31, 2022.

The principal considerations for our determination that performing procedures relating to the bankruptcy proceedings is a critical audit matter are a high degree of auditor subjectivity and effort in performing procedures and evaluating audit evidence relating to the accounting and disclosures related to the bankruptcy proceedings and the audit effort involved the use of professionals with specialized skill and knowledge.

Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming our overall opinion on the consolidated financial statements. These procedures included testing the effectiveness of controls related to management's accounting for and disclosure of the bankruptcy proceedings. These procedures also included among others, (i) reading the restructuring support agreement and evaluating the reasonableness of management's assessment of the probable loss in relation to the opioid litigation matters, (ii) testing, for a sample of transactions, the completeness and accuracy of the classification of transactions as liabilities subject to compromise or reorganization items, net, (iii) obtaining and evaluating letters of audit inquiry with internal and external legal counsel related to opioid litigation and the bankruptcy proceedings and (iv) evaluating, on a sample basis, management's accounting for claims submitted to the bankruptcy court. Professionals with specialized skill and knowledge were used to assist in evaluating the completeness and accuracy of amounts classified as liabilities subject to compromise and reorganization items, net. These procedures also included evaluating the accuracy of the Company's disclosures with respect to the bankruptcy proceedings.

/s/ PricewaterhouseCoopers LLP

Philadelphia, Pennsylvania
March 6, 2023

We have served as the Company's auditor since 2014.

ENDO INTERNATIONAL PLC
(DEBTOR-IN-POSSESSION)
CONSOLIDATED BALANCE SHEETS
DECEMBER 31, 2022 AND 2021
(Dollars in thousands, except share and per share data)

	December 31, 2022	December 31, 2021
ASSETS		
CURRENT ASSETS:		
Cash and cash equivalents	$ 1,018,883	$ 1,507,196
Restricted cash and cash equivalents	145,358	124,114
Accounts receivable, net	493,988	592,019
Inventories, net	274,499	283,552
Prepaid expenses and other current assets	136,923	200,484
Income taxes receivable	7,117	7,221
Total current assets	$ 2,076,768	$ 2,714,586
PROPERTY, PLANT AND EQUIPMENT, NET	438,314	396,712
OPERATING LEASE ASSETS	28,070	34,832
GOODWILL	1,352,011	3,197,011
OTHER INTANGIBLES, NET	1,732,935	2,362,823
DEFERRED INCOME TAXES	—	1,138
OTHER ASSETS	129,839	60,313
TOTAL ASSETS	$ 5,757,937	$ 8,767,415
LIABILITIES AND SHAREHOLDERS' DEFICIT		
CURRENT LIABILITIES:		
Accounts payable and accrued expenses	$ 687,183	$ 836,898
Current portion of legal settlement accrual	—	580,994
Current portion of operating lease liabilities	903	10,992
Current portion of long-term debt	—	200,342
Income taxes payable	1,541	736
Total current liabilities	$ 689,627	$ 1,629,962
DEFERRED INCOME TAXES	13,825	21,628
LONG-TERM DEBT, LESS CURRENT PORTION, NET	—	8,048,980
OPERATING LEASE LIABILITIES, LESS CURRENT PORTION	5,129	33,727
OTHER LIABILITIES	42,746	277,104
LIABILITIES SUBJECT TO COMPROMISE	9,168,782	—
COMMITMENTS AND CONTINGENCIES (NOTE 16)		
SHAREHOLDERS' DEFICIT:		
Euro deferred shares, $0 01 par value; 4,000,000 shares authorized and issued at both December 31, 2022 and December 31, 2021	43	45
Ordinary shares, $0 0001 par value; 1,000,000,000 shares authorized; 235,208,039 and 233,690,816 shares issued and outstanding at December 31, 2022 and December 31, 2021, respectively	24	23
Additional paid-in capital	8,969,322	8,953,906
Accumulated deficit	(12,904,620)	(9,981,515)
Accumulated other comprehensive loss	(226,941)	(216,445)
Total shareholders' deficit	$ (4,162,172)	$ (1,243,986)
TOTAL LIABILITIES AND SHAREHOLDERS' DEFICIT	$ 5,757,937	$ 8,767,415

See accompanying Notes to Consolidated Financial Statements

ENDO INTERNATIONAL PLC
(DEBTOR-IN-POSSESSION)
CONSOLIDATED STATEMENTS OF OPERATIONS
YEARS ENDED DECEMBER 31, 2022, 2021 AND 2020
(Dollars and shares in thousands, except per share data)

	2022	2021	2020
TOTAL REVENUES, NET	$ 2,318,875	$ 2,993,206	$ 2,903,074
COSTS AND EXPENSES:			
Cost of revenues	1,092,499	1,221,064	1,442,511
Selling, general and administrative	777,169	861,760	698,506
Research and development	128,033	123,440	125,573
Acquired in-process research and development	68,700	25,120	33,329
Litigation-related and other contingencies, net	478,722	345,495	(19,049)
Asset impairment charges	2,142,746	414,977	120,344
Acquisition-related and integration items, net	408	(8,379)	16,549
Interest expense, net	349,776	562,353	532,939
Loss on extinguishment of debt	—	13,753	—
Reorganization items, net	202,978	—	—
Other income, net	(34,054)	(19,774)	(21,110)
LOSS FROM CONTINUING OPERATIONS BEFORE INCOME TAX	$ (2,888,102)	$ (546,603)	$ (26,518)
INCOME TAX EXPENSE (BENEFIT)	21,516	22,478	(273,982)
(LOSS) INCOME FROM CONTINUING OPERATIONS	$ (2,909,618)	$ (569,081)	$ 247,464
DISCONTINUED OPERATIONS, NET OF TAX (NOTE 4)	(13,487)	(44,164)	(63,520)
NET (LOSS) INCOME	$ (2,923,105)	$ (613,245)	$ 183,944
NET (LOSS) INCOME PER SHARE—BASIC:			
Continuing operations	$ (12 39)	$ (2 44)	$ 1 08
Discontinued operations	(0 06)	(0 19)	(0 28)
Basic	$ (12 45)	$ (2 63)	$ 0 80
NET (LOSS) INCOME PER SHARE—DILUTED:			
Continuing operations	$ (12 39)	$ (2 44)	$ 1 06
Discontinued operations	(0 06)	(0 19)	(0 27)
Diluted	$ (12 45)	$ (2 63)	$ 0 79
WEIGHTED AVERAGE SHARES:			
Basic	234,840	232,785	229,314
Diluted	234,840	232,785	233,653

See accompanying Notes to Consolidated Financial Statements

ENDO INTERNATIONAL PLC
(DEBTOR-IN-POSSESSION)
CONSOLIDATED STATEMENTS OF COMPREHENSIVE (LOSS) INCOME
YEARS ENDED DECEMBER 31, 2022, 2021 AND 2020
(Dollars in thousands)

	2022	2021	2020
NET (LOSS) INCOME	$ (2,923,105)	$ (613,245)	$ 183,944
OTHER COMPREHENSIVE (LOSS) INCOME:			
Net unrealized (loss) gain on foreign currency	$ (10,496)	$ 1,308	$ 1,337
Total other comprehensive (loss) income	$ (10,496)	$ 1,308	$ 1,337
COMPREHENSIVE (LOSS) INCOME	$ (2,933,601)	$ (611,937)	$ 185,281

See accompanying Notes to Consolidated Financial Statements

ENDO INTERNATIONAL PLC
(DEBTOR-IN-POSSESSION)
CONSOLIDATED STATEMENTS OF SHAREHOLDERS' DEFICIT
YEARS ENDED DECEMBER 31, 2022, 2021 AND 2020
(Dollars in thousands, except share data)

	Ordinary Shares		Euro Deferred Shares		Additional Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive Loss	Total Shareholders' Deficit
	Number of Shares	Amount	Number of Shares	Amount				
BALANCE, DECEMBER 31, 2019	226,802,609	$ 23	4,000,000	$ 45	$ 8,904,692	$ (9,552,214)	$ (219,090)	$ (866,544)
Net income	—	—	—	—	—	183,944	—	183,944
Other comprehensive income	—	—	—	—	—	—	1,337	1,337
Compensation related to share-based awards	—	—	—	—	41,357	—	—	41,357
Ordinary shares issued	3,513,159	—	—	—	—	—	—	—
Tax withholding for restricted shares	—	—	—	—	(8,036)	—	—	(8,036)
Other	—	—	—	4	(1)	—	—	3
BALANCE, DECEMBER 31, 2020	230,315,768	$ 23	4,000,000	$ 49	$ 8,938,012	$ (9,368,270)	$ (217,753)	$ (647,939)
Net loss	—	—	—	—	—	(613,245)	—	(613,245)
Other comprehensive income	—	—	—	—	—	—	1,308	1,308
Compensation related to share-based awards	—	—	—	—	30,046	—	—	30,046
Exercise of options	82,331	—	—	—	622	—	—	622
Ordinary shares issued	3,292,717	—	—	—	—	—	—	—
Tax withholding for restricted shares	—	—	—	—	(14,774)	—	—	(14,774)
Other	—	—	—	(4)	—	—	—	(4)
BALANCE, DECEMBER 31, 2021	233,690,816	$ 23	4,000,000	$ 45	$ 8,953,906	$ (9,981,515)	$ (216,445)	$ (1,243,986)
Net loss	—	—	—	—	—	(2,923,105)	—	(2,923,105)
Other comprehensive loss	—	—	—	—	—	—	(10,496)	(10,496)
Compensation related to share-based awards	—	—	—	—	17,314	—	—	17,314
Ordinary shares issued	1,517,223	1	—	—	(1)	—	—	—
Tax withholding for restricted shares	—	—	—	—	(1,898)	—	—	(1,898)
Other	—	—	—	(2)	1	—	—	(1)
BALANCE, DECEMBER 31, 2022	235,208,039	$ 24	4,000,000	$ 43	$ 8,969,322	$ (12,904,620)	$ (226,941)	$ (4,162,172)

See accompanying Notes to Consolidated Financial Statements

ENDO INTERNATIONAL PLC
(DEBTOR-IN-POSSESSION)
CONSOLIDATED STATEMENTS OF CASH FLOWS
YEARS ENDED DECEMBER 31, 2022, 2021 AND 2020
(Dollars in thousands)

	2022	2021	2020
OPERATING ACTIVITIES:			
Net (loss) income	$ (2,923,105)	$ (613,245)	$ 183,944
Adjustments to reconcile Net (loss) income to Net cash provided by operating activities:			
Depreciation and amortization	391,629	457,098	518,807
Share-based compensation	17,314	30,046	41,357
Amortization of debt issuance costs and discount	9,406	14,437	15,606
Deferred income taxes	(7,303)	(3,157)	(163,558)
Change in fair value of contingent consideration	408	(8,793)	16,353
Loss (gain) on extinguishment of debt	—	13,753	—
Acquired in-process research and development charges	68,700	25,120	33,329
Asset impairment charges	2,142,746	414,977	120,344
Non-cash reorganization items, net	89,197	—	—
Gain on sale of business and other assets	(26,183)	(4,516)	(16,353)
Other	2,776	—	—
Changes in assets and liabilities which provided (used) cash:			
Accounts receivable	105,912	(82,052)	(45,792)
Inventories	(4,359)	48,978	(8,031)
Prepaid and other assets	80,350	(34,002)	(27,421)
Accounts payable, accrued expenses and other liabilities	321,055	84,391	(171,366)
Income taxes payable/receivable, net	650	68,015	(95,100)
Net cash provided by operating activities	$ 269,193	$ 411,050	$ 402,119
INVESTING ACTIVITIES:			
Capital expenditures, excluding capitalized interest	(99,722)	(77,929)	(69,971)
Capitalized interest payments	(3,140)	(2,721)	(2,892)
Proceeds from the U S Government Agreement	18,635	—	—
Acquisitions, including in-process research and development, net of cash and restricted cash acquired	(90,320)	(5,000)	(654,231)
Proceeds from sales and maturities of investments	—	—	92,763
Product acquisition costs and license fees	—	(4,177)	(2,000)
Proceeds from sale of business and other assets, net	41,400	30,283	6,737
Net cash used in investing activities	$ (133,147)	$ (59,544)	$ (629,594)

ENDO INTERNATIONAL PLC
(DEBTOR-IN-POSSESSION)
CONSOLIDATED STATEMENTS OF CASH FLOWS
YEARS ENDED DECEMBER 31, 2022, 2021 AND 2020
(Dollars in thousands)

	2022	2021	2020
FINANCING ACTIVITIES:			
Proceeds from issuance of notes, net	—	1,279,978	—
Proceeds from issuance of term loans, net	—	1,980,000	—
Repayments of notes	(180,342)	—	(57,649)
Repayments of term loans	(10,000)	(3,310,475)	(34,150)
Repayments of revolving debt	—	(22,800)	—
Adequate protection payments	(313,109)	—	—
Repayments of other indebtedness	(6,062)	(5,448)	(4,884)
Payments for debt issuance and extinguishment costs	—	(8,574)	—
Payments for contingent consideration	(2,462)	(4,010)	(3,848)
Payments of tax withholding for restricted shares	(1,898)	(14,774)	(8,036)
Proceeds from exercise of options	—	622	—
Net cash used in financing activities	$ (513,873)	$ (105,481)	$ (108,567)
Effect of foreign exchange rate	(4,242)	285	654
NET (DECREASE) INCREASE IN CASH, CASH EQUIVALENTS, RESTRICTED CASH AND RESTRICTED CASH EQUIVALENTS	$ (382,069)	$ 246,310	$ (335,388)
CASH, CASH EQUIVALENTS, RESTRICTED CASH AND RESTRICTED CASH EQUIVALENTS, BEGINNING OF PERIOD	1,631,310	1,385,000	1,720,388
CASH, CASH EQUIVALENTS, RESTRICTED CASH AND RESTRICTED CASH EQUIVALENTS, END OF PERIOD	$ 1,249,241	$ 1,631,310	$ 1,385,000
SUPPLEMENTAL INFORMATION:			
Cash paid for interest, excluding capitalized interest and adequate protection payments	$ 289,664	$ 538,424	$ 534,529
Cash paid for income taxes, gross	$ 14,101	$ 10,019	$ 11,669
Cash refunds from income taxes, gross	$ 3,092	$ 57,801	$ 31,897
SCHEDULE OF NONCASH INVESTING AND FINANCING ACTIVITIES:			
Acquisitions, including in-process research and development, accrued in the period but not yet paid	$ —	$ 20,120	$ —

See accompanying Notes to Consolidated Financial Statements

ENDO INTERNATIONAL PLC
(DEBTOR-IN-POSSESSION)
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS
FOR THE YEARS ENDED DECEMBER 31, 2022, 2021 AND 2020

NOTE 1. DESCRIPTION OF BUSINESS

Background and Basis of Presentation

Endo International plc is an Ireland-domiciled specialty pharmaceutical company that conducts business through its operating subsidiaries. Unless otherwise indicated or required by the context, references throughout to "Endo," the "Company," "we," "our" or "us" refer to Endo International plc and its subsidiaries. The accompanying Consolidated Financial Statements of Endo International plc and its subsidiaries have been prepared in accordance with U.S. GAAP.

Going Concern

As further discussed herein, thousands of governmental and private plaintiffs have filed suit against us and/or certain of our subsidiaries alleging opioid-related claims, most of which we have not been able to settle. As a result of the possibility or occurrence of an unfavorable outcome with respect to these proceedings, other legal proceedings and certain other risks and uncertainties, we have been exploring a wide array of potential actions as part of our contingency planning and, as further described in the Second-Quarter 2022 Form 10-Q, we previously concluded that the related conditions and events gave rise to substantial doubt about our ability to continue as a going concern.

Subsequent to the filing of the Second-Quarter 2022 Form 10-Q, on the August 16, 2022 Petition Date, the Debtors filed voluntary petitions for relief under the Bankruptcy Code, which constituted an event of default that accelerated our obligations under substantially all of our then-outstanding debt instruments. However, section 362 of the Bankruptcy Code stays creditors from taking any action to enforce the related financial obligations and creditors' rights of enforcement in respect of the debt instruments are subject to the applicable provisions of the Bankruptcy Code. Refer to Note 2. Bankruptcy Proceedings and Note 15. Debt for additional information. As a result of these conditions and events, management continues to believe there is substantial doubt about our ability to continue as a going concern within one year after the date of issuance of these Consolidated Financial Statements. The accompanying Consolidated Financial Statements have been prepared under the going concern basis of accounting as required by U.S. GAAP and do not include any adjustments that might be necessary should we be unable to continue as a going concern.

NOTE 2. BANKRUPTCY PROCEEDINGS

Chapter 11 Filing

As noted above, on the Petition Date, the Debtors filed voluntary petitions for relief under the Bankruptcy Code. The Debtors have received approval from the U.S. Bankruptcy Court for the Southern District of New York (the Bankruptcy Court) to jointly administer their chapter 11 cases (the Chapter 11 Cases) for administrative purposes only pursuant to Rule 1015(b) of the Federal Rules of Bankruptcy Procedure under the caption *In re Endo International plc, et al*. Certain entities consolidated by Endo International plc and included in these Consolidated Financial Statements are not party to the Chapter 11 Cases. These entities are collectively referred to herein as the Non-Debtor Affiliates.

The Debtors will continue to operate their businesses and manage their properties as debtors-in-possession pursuant to sections 1107 and 1108 of the Bankruptcy Code. As debtors-in-possession, the Debtors are generally permitted to continue to operate as ongoing businesses and pay debts and honor obligations arising in the ordinary course of their businesses after the Petition Date. However, the Debtors generally may not pay third-party claims or creditors on account of obligations arising before the Petition Date or engage in transactions outside the ordinary course of business without approval of the Bankruptcy Court. Under the Bankruptcy Code, third-party actions to collect pre-petition indebtedness owed by the Debtors, as well as most litigation pending against the Debtors as of the Petition Date, are generally subject to an automatic stay. However, under the Bankruptcy Code, certain legal proceedings, such as those involving the assertion of a governmental entity's police or regulatory powers, may not be subject to the automatic stay and may continue unless otherwise ordered by the Bankruptcy Court.

Among other requirements, chapter 11 proceedings must comply with the priority scheme established by the Bankruptcy Code, under which certain post-petition and secured or "priority" pre-petition liabilities generally need to be satisfied before general unsecured creditors and shareholders are entitled to receive any distribution.

Under the Bankruptcy Code, the Debtors may assume, modify, assign or reject certain executory contracts and unexpired leases, including, without limitation, leases of real property and equipment, subject to the approval of the Bankruptcy Court and certain other conditions. Generally, the rejection of an executory contract or unexpired lease is treated as a pre-petition breach of such executory contract or unexpired lease and, subject to certain exceptions, relieves the Debtors from performing their future obligations under such executory contract or unexpired lease but entitles the contract counterparty or lessor to a pre-petition general unsecured claim for damages caused by such deemed breach. Generally, the assumption of an executory contract or unexpired lease requires the Debtors to cure existing monetary defaults under such executory contract or unexpired lease and provide adequate assurance of future performance. Accordingly, any description of an executory contract or unexpired lease in this report, including, where applicable, the express termination rights thereunder or a quantification of obligations, must be read in conjunction with, and is qualified by, any overriding rejection rights the Debtors have under the Bankruptcy Code.

To ensure their ability to continue operating in the ordinary course of business, the Debtors have filed with the Bankruptcy Court a variety of motions seeking “first day” relief, including the authority to access cash collateral, continue using their cash management system, pay employee wages and benefits and pay vendors in the ordinary course of business. At a hearing held on August 18, 2022, the Bankruptcy Court generally approved the relief sought in these motions on an interim basis. Following subsequent hearings held on September 28, 2022, October 13, 2022 and October 19, 2022, the Bankruptcy Court entered orders approving substantially all of the relief sought on a final basis.

Events of Default

The August 16, 2022 bankruptcy filings by the Debtors constituted an event of default that accelerated our obligations under substantially all of our then-outstanding debt instruments. However, section 362 of the Bankruptcy Code stays creditors from taking any action to enforce the related financial obligations and creditors’ rights of enforcement in respect of the debt instruments are subject to the applicable provisions of the Bankruptcy Code. Refer to Note 15. Debt for additional information.

Restructuring Support Agreement

On August 16, 2022, we entered into a Restructuring Support Agreement (the RSA) with an ad hoc group (the Ad Hoc First Lien Group) of certain creditors holding in excess of 50% of the aggregate outstanding principal amount of Secured Debt (as defined in that certain collateral trust agreement, dated as of April 27, 2017, among Endo International plc, certain subsidiaries of Endo International plc, the other grantors from time to time party thereto, JPMorgan Chase Bank, N.A., as administrative agent under the Credit Agreement, and Wells Fargo Bank, National Association, as indenture trustee, and Wilmington Trust, National Association, as collateral trustee (the Collateral Trust Agreement)), pursuant to which, among other things, one or more entities formed in a manner acceptable to the Ad Hoc First Lien Group (the Stalking Horse Bidder or the Purchaser) will serve as stalking horse bidder as we seek to sell all or substantially all of our assets in a sale pursuant to section 363 of the Bankruptcy Code (the Sale).

As described in the RSA, the Stalking Horse Bidder’s bid (the Stalking Horse Bid), which is subject to higher or otherwise better bids from other parties, includes an offer to purchase substantially all of our assets for an aggregate purchase price including: (i) a credit bid in full satisfaction of the Prepetition First Lien Indebtedness (as defined in the RSA); (ii) $5 million in cash on account of certain unencumbered assets; (iii) $122 million to wind-down our operations following the Sale closing date (the Wind-Down Amount); (iv) pre-closing professional fees; and (v) the assumption of certain liabilities. As part of the Stalking Horse Bid, the Stalking Horse Bidder will also make offers of employment to all of our active employees. Pursuant to the RSA, the definitive purchase and sale agreement with respect to the Stalking Horse Bid will include customary representations and warranties and customary covenants by the parties thereto. On November 23, 2022, we filed: (i) a motion seeking Bankruptcy Court approval of bidding procedures in connection with the Sale and (ii) a motion seeking to set deadlines for all claimants to file claims against the Debtors. Although both motions were initially set to be heard by the Bankruptcy Court at a hearing on December 15, 2022, following several conferences with both the Bankruptcy Court and all major parties in interest in the Chapter 11 Cases, the hearing on both motions was adjourned to allow the Debtors and certain key parties in the Chapter 11 Cases to participate in a mediation process to attempt to resolve certain objections and contested issues relating to the Sale and other critical matters in the Chapter 11 Cases. On March 3, 2023, the Debtors announced that, as a result of the mediation process, the Ad Hoc First Lien Group (and Stalking Horse Bidder) had reached certain resolutions in principle with both the unsecured creditors’ committee and opioid claimants’ committee appointed in the Chapter 11 Cases and certain ad hoc groups of debtholders. These resolutions, which remain subject to definitive documentation, are supported by the Debtors. In connection with such resolutions, the Company agreed in principle with the Ad Hoc First Lien Group to reduce the Wind-Down Amount associated with the Stalking Horse Bid from $122 million to approximately $115 million, subject to definitive documentation. As negotiations among the mediation parties continue, the mediation has been extended and remains ongoing and the Bankruptcy Court hearing on both motions has been adjourned to an undetermined date. As a result of such adjournment, the proposed timelines and deadlines set forth in both motions are expected to be extended.

The RSA contemplates a marketing process and auction that will be conducted under the supervision of the Bankruptcy Court, during which interested parties will have an opportunity to conduct due diligence and determine whether to submit a bid to acquire the Debtors' assets. If the Stalking Horse Bid is selected as the highest or otherwise best offer following said marketing process and auction, the Ad Hoc First Lien Group will direct the Collateral Trustee (as defined in the Collateral Trust Agreement) to assign its rights to credit bid, on behalf of the Secured Parties (as defined in the Collateral Trust Agreement), to the Stalking Horse Bidder, so as to enable the Stalking Horse Bidder to credit bid for all or substantially all of our assets in exchange for the extinguishment of the obligations to the Secured Parties. The RSA further contemplates that the Purchaser will fund one or more trusts for parties with opioid-related claims against us, as further discussed in Note 16. Commitments and Contingencies.

Pursuant to the RSA, each of the parties agreed to, among other things, take all actions as are necessary and appropriate to facilitate the implementation and consummation of the Restructuring (as defined in the RSA), negotiate in good faith certain definitive documents relating to the Restructuring and obtain required approvals. In addition, we agreed to conduct our business in the ordinary course, provide notice and certain materials relating to the Restructuring to the consenting creditors' advisors and pay certain fees and expenses of the consenting creditors.

The RSA provides certain milestones for the Restructuring. If we fail to satisfy these milestones and such failure is not the result of a breach of the RSA by the Required Consenting First Lien Creditors (as defined in the RSA), the Required Consenting First Lien Creditors will have the right to terminate the RSA. These milestones, as modified since we entered into the RSA (and which may be further modified from time to time), include: (i) not later than 11:59 p.m. prevailing Eastern Time on October 25, 2022, the Bankruptcy Court shall have entered the Cash Collateral Order on a final basis; (ii) not later than 11:59 p.m. prevailing Eastern Time on March 16, 2023, the Bankruptcy Court shall have entered an order approving the bidding procedures; (iii) not later than 11:59 p.m. prevailing Eastern Time on September 13, 2023, the Bankruptcy Court shall have entered an order approving the Sale; and (iv) not later than 11:59 p.m. prevailing Eastern Time on September 13, 2023 (the Outside Date), the closing of the Sale shall have occurred, subject to certain extensions of the Outside Date as set forth in the RSA, including: (a) for extensions of prior milestones; (b) to close the Sale transaction with a backup bidder; and (c) for delays in obtaining regulatory or third-party approvals or consents.

Each of the parties to the RSA may terminate the agreement (and thereby their support for the Sale) under certain limited circumstances, including for material breaches and materially untrue representations and warranties by their counterparties, if a governmental agency enjoins the Sale or if the purchase and sale agreement with respect to the Sale is terminated under certain circumstances.

The transactions contemplated by the RSA are subject to approval by the Bankruptcy Court, among other conditions. Accordingly, no assurance can be given that the transactions described therein will be consummated.

The Chapter 11 Proceedings

Cash Collateral

In October 2022, the Bankruptcy Court entered the Cash Collateral Order approving the Debtors' consensual use of their secured creditors' cash collateral. The Debtors intend to use the cash collateral to, among other things, permit the orderly continuation of their businesses, pay the costs of administration of their estates and satisfy other working capital and general corporate purposes. As described in additional detail elsewhere in this report, including in Note 15. Debt, the Cash Collateral Order obligates the Debtors to make certain adequate protection payments during the bankruptcy proceedings, establishes a budget for the Debtors' use of cash collateral, establishes certain informational rights for the Debtors' secured creditors and provides for the waiver of certain Bankruptcy Code provisions. The Cash Collateral Order also requires the Debtors to maintain at least $600.0 million of "liquidity," calculated at the end of each week as unrestricted cash and cash equivalents plus certain specified amounts of restricted cash associated with the TLC Agreement, which is further discussed below in Note 12. License, Collaboration and Asset Acquisition Agreements.

Potential Claims

In November 2022, the Debtors filed with the Bankruptcy Court schedules and statements, subject to further amendment or modification, which set forth, among other things, the assets and liabilities of each of the Debtors, subject to the assumptions filed in connection therewith.

As part of the Chapter 11 Cases, persons and entities believing that they have claims or causes of action against the Debtors may file proofs of claim evidencing such claims. As noted above, the Debtors have filed a motion seeking to set a bar date (deadline) for holders of claims to file proofs of claim (including general claims and claims of governmental units), which motion has been adjourned to an undetermined date.

The Debtors have received numerous claims as of the date of this report including, in certain cases, duplicate claims across multiple Debtors. For example, the IRS has filed multiple proofs of claim against several of the Debtors, as further discussed in Note 21. Income Taxes. We expect that the Debtors may continue to receive a significant number of claims in the future. As claims are filed, they are being evaluated for validity and compared to amounts recorded in our accounting records. As of the date of this report, the amounts of certain of the claims received exceed the amounts of the corresponding liabilities, if any, that we have recorded based on our assessments of the purported liabilities underlying such claims, and it is likely this will continue to be the case in future periods. We are not aware of any claims that we currently expect will require a material adjustment to the accounts and balances as reported as of December 31, 2022.

Differences in amounts recorded and claims filed by creditors will continue to be investigated and resolved, including through the filing of objections with the Bankruptcy Court, where appropriate. The Debtors may ask the Bankruptcy Court to disallow claims that the Debtors believe are duplicative, have been later amended or superseded, are without merit, are overstated or should be disallowed for other reasons. In addition, as a result of this process, the Debtors may identify additional liabilities that will need to be recorded or reclassified to Liabilities subject to compromise in the Consolidated Balance Sheets. In light of the substantial number of claims that may be filed, the claims resolution process may take considerable time to complete and may continue for the duration of the Debtors' bankruptcy proceedings.

Subsequent Developments

The Bankruptcy Court adjourned the hearings for certain critical motions filed in November and December 2022, including: (i) our motion to establish bidding procedures in connection with the Sale; (ii) our motion to establish deadlines for creditors to file proofs of claim; and (iii) our motion to extend our exclusive periods to file and solicit a plan of reorganization, in order to allow the Debtors and certain key parties in the Chapter 11 Cases to participate in a mediation process to attempt to resolve certain objections and contested issues relating to the Sale and other critical matters. On March 3, 2023, the Debtors announced that, as a result of the mediation process, the Ad Hoc First Lien Group (and Stalking Horse Bidder) had reached certain resolutions in principle with both the unsecured creditors' committee and opioid claimants' committee appointed in the Chapter 11 Cases and certain ad hoc groups of debtholders. These resolutions, which remain subject to definitive documentation, are supported by the Debtors. In connection with such resolutions, the mediation has been extended and remains ongoing and the Bankruptcy Court hearing on the three motions has been adjourned to an undetermined date.

Bankruptcy Accounting

As a result of the Chapter 11 Cases, we have applied the provisions of ASC 852 in preparing the accompanying Consolidated Financial Statements. ASC 852 requires that, for periods including and after the filing of a chapter 11 petition, the Consolidated Financial Statements distinguish transactions and events that are directly associated with the reorganization from the ongoing operations of the business.

Accordingly, for periods beginning with the third quarter of 2022, pre-petition unsecured and undersecured claims related to the Debtors that may be impacted by the bankruptcy reorganization process have been classified as Liabilities subject to compromise in the Consolidated Balance Sheets. Liabilities subject to compromise include pre-petition liabilities for which there is uncertainty about whether such pre-petition liabilities could be impaired as a result of the Chapter 11 Cases. Liabilities subject to compromise are recorded at the expected amount of the total allowed claim, even if they may ultimately be settled for different amounts. The following table sets forth, as of December 31, 2022, information about the amounts presented as Liabilities subject to compromise in our Consolidated Balance Sheets (in thousands):

	December 31, 2022
Accounts payable	$ 30,317
Accrued interest	160,617
Debt	7,834,717
Litigation accruals	820,805
Uncertain tax positions	235,176
Other (1)	87,150
Total	$ 9,168,782

(1) Amounts include operating and finance lease liabilities as further described in Note 9 Leases, acquisition-related contingent consideration liabilities as further described in Note 7 Fair Value Measurements and a variety of other miscellaneous liabilities

The determination of how liabilities will ultimately be settled or treated cannot be made until approved by the Bankruptcy Court. Therefore, the amounts in the table above are preliminary and may be subject to future adjustments as a result of, among other things, the possibility or occurrence of certain Bankruptcy Court actions, further developments with respect to disputed claims, any rejection by us of executory contracts and/or any payments by us of amounts classified as Liabilities subject to compromise, which may be allowed in certain limited circumstances. Amounts are also subject to adjustments if we make changes to our assumptions or estimates related to claims as additional information becomes available to us including, without limitation, those related to the expected amounts of allowed claims, the value of any collateral securing claims and the secured status of claims. Such adjustments may be material. Additionally, as a result of our ongoing bankruptcy proceedings, we may sell or otherwise dispose of or liquidate assets or settle liabilities for amounts other than those reflected in the accompanying Consolidated Financial Statements. The possibility or occurrence of any such actions could materially impact the amounts and classifications of such assets and liabilities reported in our Consolidated Balance Sheets and could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Certain expenses, gains and losses resulting from and recognized during our bankruptcy proceedings are now being recorded in Reorganization items, net in our Consolidated Statements of Operations. The following table sets forth, for the year ended December 31, 2022, information about the amounts presented as Reorganization items, net in our Consolidated Statements of Operations (in thousands):

	2022
Professional fees	$ 113,781
Debt valuation adjustments	89,197
Total	$ 202,978

Since the Petition Date, our operating cash flows included net cash outflows of $53.7 million related to amounts classified or expected to be classified as Reorganization items, net, which primarily consisted of payments for professional fees.

Refer also to Note 15. Debt for information about how our bankruptcy proceedings and certain related developments have affected our debt service payments and how such payments are being reflected in our Consolidated Financial Statements.

Nasdaq Delisting

On August 17, 2022, we received a letter (the Notice) from Nasdaq stating that, in accordance with Nasdaq Listing Rules 5101, 5110(b) and IM-5101-1, Nasdaq had determined that Endo's ordinary shares would be delisted. In accordance with the Notice, trading of Endo's ordinary shares was suspended at the opening of business on August 26, 2022. As a result, Endo's ordinary shares began trading exclusively on the over-the-counter market on August 26, 2022. On the over-the-counter market, Endo's ordinary shares, which previously traded on the Nasdaq Global Select Market under the symbol ENDP, began to trade under the symbol ENDPQ. On September 14, 2022, Nasdaq filed a Form 25-NSE with the SEC and Endo's ordinary shares were subsequently delisted from the Nasdaq Global Select Market. On December 13, 2022, Endo's ordinary shares were deregistered under Section 12(b) of the Exchange Act.

NOTE 3. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Significant Accounting Policies

Consolidation and Basis of Presentation. The Consolidated Financial Statements include the accounts of wholly-owned subsidiaries after the elimination of intercompany accounts and transactions.

Reclassifications. Certain prior period amounts have been reclassified to conform to the current period presentation. The reclassification adjustments primarily relate to changes to the presentation of certain costs and expenses in our Consolidated Statements of Operations. Specifically, effective with the first quarter of 2022, the Company has added a new financial statement line item labeled Acquired in-process research and development. Any prior period amounts of acquired in-process research and development charges presented in this report have been reclassified to this line item from the existing financial statement line item labeled Research and development.

Bankruptcy Accounting. Refer to Note 2. Bankruptcy Proceedings under the heading "Bankruptcy Accounting" for a discussion of accounting considerations related to our ongoing bankruptcy proceedings.

Use of Estimates. The preparation of our Consolidated Financial Statements in conformity with U.S. GAAP requires us to make estimates and assumptions that affect the amounts and disclosures in our Consolidated Financial Statements, including the Notes thereto, and elsewhere in this report. For example, we are required to make significant estimates and assumptions related to revenue recognition, including sales deductions, long-lived assets, goodwill, other intangible assets, income taxes, contingencies, financial instruments, share-based compensation, liabilities subject to compromise and reorganization items, net, among others. Some of these estimates can be subjective and complex. Uncertainties related to the continued magnitude and duration of the COVID-19 pandemic, the extent to which it will impact our estimated future financial results, worldwide macroeconomic conditions including interest rates, employment rates, consumer spending, health insurance coverage, the speed of the anticipated recovery and governmental and business reactions to the pandemic, including any possible re-initiation of shutdowns or renewed restrictions, have increased the complexity of developing these estimates, including the allowance for expected credit losses and the carrying amounts of long-lived assets, goodwill and other intangible assets. Additionally, as a result of our ongoing bankruptcy proceedings, we may sell or otherwise dispose of or liquidate assets or settle liabilities for amounts other than those reflected in the accompanying Consolidated Financial Statements. The possibility or occurrence of any such actions could materially impact the amounts and classifications of such assets and liabilities reported in our Consolidated Balance Sheets. Furthermore, our ongoing bankruptcy proceedings and planned sale process have resulted in and are likely to continue to result in significant changes to our business, which could ultimately result in, among other things, asset impairment charges that may be material. Although we believe that our estimates and assumptions are reasonable, there may be other reasonable estimates or assumptions that differ significantly from ours. Further, our estimates and assumptions are based upon information available at the time they were made. Actual results may differ significantly from our estimates, including as a result of the uncertainties described in this report, those described in our other reports filed with the SEC or other uncertainties.

We regularly evaluate our estimates and assumptions using historical experience and other factors, including the economic environment. As future events and their effects cannot be determined with precision, our estimates and assumptions may prove to be incomplete or inaccurate, or unanticipated events and circumstances may occur that might cause us to change those estimates and assumptions. Market conditions, such as illiquid credit markets, volatile equity markets, dramatic fluctuations in foreign currency rates and economic downturns, can increase the uncertainty already inherent in our estimates and assumptions. We also are subject to other risks and uncertainties that may cause actual results to differ from estimated amounts, such as changes in the healthcare environment, competition, litigation, legislation and regulations. We adjust our estimates and assumptions when facts and circumstances indicate the need for change. Those changes generally will be reflected in our Consolidated Financial Statements on a prospective basis.

Customer, Product and Supplier Concentration. We primarily sell our products to wholesalers, retail drug store chains, supermarket chains, mass merchandisers, distributors, mail order accounts, hospitals and/or government agencies. Our wholesalers and/or distributors purchase products from us and, in turn, supply products to retail drug store chains, independent pharmacies, hospitals, long-term care facilities, clinics, home infusion pharmacies, government facilities and MCOs. Net revenues from direct customers that accounted for 10% or more of our total consolidated net revenues during the years ended December 31, 2022, 2021 and 2020 are as follows:

	2022	2021	2020
AmerisourceBergen Corporation	35 %	36 %	33 %
McKesson Corporation	26 %	32 %	27 %
Cardinal Health, Inc.	20 %	22 %	24 %

Revenues from these customers are included within each of our segments.

XIAFLEX® accounted for 19%, 14% and 11% of our 2022, 2021 and 2020 net revenues, respectively. Varenicline tablets (our generic version of Pfizer Inc.'s Chantix®) accounted for 13% of our 2022 net revenues. VASOSTRICT® accounted for 11%, 30% and 27% of our 2022, 2021 and 2020 net revenues, respectively. No other products accounted for 10% or more of our net revenues during any of the years ended December 31, 2022, 2021 and 2020.

We have agreements with certain third parties for the manufacture, supply and processing of certain of our existing pharmaceutical products. See Note 16. Commitments and Contingencies for information on any material manufacturing, supply and other service agreements.

We are subject to risks and uncertainties associated with these concentrations that could have a material adverse effect on our business, financial condition, results of operations and cash flows in future periods, including in the near term.

Revenue Recognition and Sales Deductions. With respect to contracts with commercial substance that establish payment terms and each party's rights regarding goods or services to be transferred, we recognize revenue when (or as) we satisfy our performance obligations for such contracts by transferring control of the underlying promised goods or services to our customers, to the extent collection of substantially all of the related consideration is probable. The amount of revenue we recognize reflects our estimate of the consideration we expect to be entitled to receive, subject to certain constraints, in exchange for such goods or services. This amount is referred to as the transaction price.

Our revenue consists almost entirely of sales of our products to customers, whereby we ship products to a customer pursuant to a purchase order. For contracts such as these, revenue is recognized when our contractual performance obligations have been fulfilled and control has been transferred to the customer pursuant to the contract's terms, which is generally upon delivery to the customer. The amount of revenue we recognize is equal to the fixed amount of the transaction price, adjusted for our estimates of a number of significant variable components including, but not limited to, estimates for chargebacks, rebates, sales incentives and allowances, DSA and other fees for services, returns and allowances, which we collectively refer to as sales deductions.

The Company utilizes the expected value method when estimating the amount of variable consideration to include in the transaction price with respect to each of the foregoing variable components and the most likely amount method when estimating the amount of variable consideration to include in the transaction price with respect to future potential milestone payments that do not qualify for the sales- and usage-based royalty exception. Variable consideration is included in the transaction price only to the extent it is probable that a significant revenue reversal will not occur when the uncertainty associated with the variable consideration is resolved. Payment terms for these types of contracts generally fall within 30 to 120 days of invoicing.

At December 31, 2022 and 2021, our reserves for sales deductions totaled $600.2 million and $588.7 million, respectively. These amounts relate primarily to our estimates of unsettled obligations for returns and allowances, rebates and chargebacks. The most significant sales deduction reserves relate to returns, wholesaler chargebacks and rebates for the Sterile Injectables and Generic Pharmaceuticals segments. Our estimates are based on factors such as our direct and indirect customers' buying patterns and the estimated resulting contractual deduction rates, historical experience, specific known market events and estimated future trends, current contractual and statutory requirements, industry data, estimated customer inventory levels, current contract sales terms with our direct and indirect customers and other competitive factors. Significant judgment and estimation is required in developing the foregoing and other relevant assumptions. The most significant sales deductions are further described below.

Returns and Allowances—Consistent with industry practice, we maintain a return policy that allows our customers to return products within a specified period of time both subsequent to and, in certain cases, prior to the products' expiration dates. Our return policy generally allows customers to receive credit for expired products within six months prior to expiration and within between six months and one year after expiration. Our provision for returns and allowances consists of our estimates for future product returns, pricing adjustments and delivery errors.

Rebates—Our provision for rebates, sales incentives and other allowances can generally be categorized into the following four types:

- direct rebates;
- indirect rebates;
- governmental rebates, including those for Medicaid, Medicare and TRICARE, among others; and
- managed-care rebates.

We establish contracts with wholesalers, chain stores and indirect customers that provide for rebates, sales incentives, DSA fees and other allowances. Some customers receive rebates upon attaining established sales volumes. Direct rebates are generally rebates paid to direct purchasing customers based on a percentage applied to a direct customer's purchases from us, including fees paid to wholesalers under our DSAs, as described above. Indirect rebates are rebates paid to indirect customers that have purchased our products from a wholesaler or distributor under a contract with us.

We are subject to rebates on sales made under governmental and managed-care pricing programs based on relevant statutes with respect to governmental pricing programs and contractual sales terms with respect to managed-care providers and GPOs. For example, we are required to provide a discount on certain of our products to patients who fall within the Medicare Part D coverage gap, also referred to as the donut hole.

We participate in various federal and state government-managed programs whereby discounts and rebates are provided to participating government entities. For example, Medicaid rebates are amounts owed based upon contractual agreements or legal requirements with public sector (Medicaid) benefit providers after the final dispensing of the product by a pharmacy to a benefit plan participant.

Chargebacks—We market and sell products to both: (i) direct customers including wholesalers, distributors, warehousing pharmacy chains and other direct purchasing entities and (ii) indirect customers including independent pharmacies, non-warehousing chains, MCOs, GPOs, hospitals and other healthcare institutions and government entities. We enter into agreements with certain of our indirect customers to establish contract pricing for certain products. These indirect customers then independently select a wholesaler from which to purchase the products at these contracted prices. Alternatively, we may pre-authorize wholesalers to offer specified contract pricing to other indirect customers. Under either arrangement, we provide credit to the wholesaler for any difference between the contracted price with the indirect customer and the wholesaler's invoice price. Such credit is called a chargeback.

Contract Assets and Contract Liabilities. Contract assets represent our right to consideration in exchange for goods or services that we have transferred when that right is conditioned on something other than the passage of time. We record income and a corresponding contract asset when we fulfill a contractual performance obligation, but must also fulfill one or more additional performance obligations before being entitled to payment. Once our right to consideration becomes unconditional, the contract asset amount is reclassified as Accounts receivable.

Contract liabilities represent our obligation to transfer goods or services to a customer. We record a contract liability generally upon receipt of consideration in advance of fulfilling one or more of our contractual performance obligations. Upon completing each performance obligation, the corresponding contract liability amount is reversed and income is recognized.

Contract assets and liabilities related to rights and obligations arising from a single contract, or a series of contracts combined and accounted for as a single contract, are generally presented on a net basis. Contract assets and liabilities are further described in Note 13. Contract Assets and Liabilities.

Acquisitions. We evaluate acquisitions of assets and other similar transactions to assess whether or not the transaction should be accounted for as a business combination or asset acquisition by first applying a screen test to determine whether substantially all of the fair value of the gross assets acquired is concentrated in a single identifiable asset or group of similar identifiable assets. If so, the transaction is accounted for as an asset acquisition. If not, further determination is required as to whether or not we have acquired inputs and processes that have the ability to create outputs, which would meet the definition of a business. Significant judgment is required in the application of the screen test to determine whether an acquisition is a business combination or an acquisition of assets.

Acquisitions meeting the definition of business combinations are accounted for using the acquisition method of accounting, which requires that the purchase price be allocated to the net assets acquired at their respective fair values. In a business combination, any excess of the purchase price over the estimated fair values of the net assets acquired is recorded as goodwill.

For asset acquisitions, a cost accumulation model is used to determine the cost of an asset acquisition. Direct transaction costs are recognized as part of the cost of an asset acquisition. We also evaluate which elements of a transaction should be accounted for as a part of an asset acquisition and which should be accounted for separately. The cost of an asset acquisition, including transaction costs, is allocated to identifiable assets acquired and liabilities assumed based on a relative fair value basis. Goodwill is not recognized in an asset acquisition. Any difference between the cost of an asset acquisition and the fair value of the net assets acquired is allocated to the non-monetary identifiable assets based on their relative fair values.

The accounting for costs associated with acquiring in-process research and development assets, including contractual upfront and milestone payments to third parties, is further discussed below.

R&D. Expenditures for R&D are expensed as incurred and included as Research and development in the Consolidated Statements of Operations. Such expenses include, among other things, the costs of discovery research, preclinical development, early- and late-clinical development and drug formulation, clinical trials, materials and medical support of marketed products. R&D spending also includes enterprise-wide costs which support our overall R&D infrastructure. Property, plant and equipment that are acquired or constructed for R&D activities and that have alternate future uses are capitalized and depreciated over their estimated useful lives on a straight-line basis. The accounting for costs associated with acquiring in-process research and development assets, including contractual upfront and milestone payments to third parties, is further discussed below.

Cash and Cash Equivalents. The Company considers all highly liquid money market instruments with an original maturities of three months or less when purchased to be cash equivalents. At December 31, 2022 and 2021, cash equivalents were deposited in financial institutions and consisted almost entirely of immediately available fund balances. The Company maintains its cash deposits and cash equivalents with financial institutions it believes to be well-known and stable.

Restricted Cash and Cash Equivalents. Cash and cash equivalents that are restricted as to withdrawal or use under the terms of certain contractual agreements are excluded from Cash and cash equivalents in the Consolidated Balance Sheets. For additional information see Note 7. Fair Value Measurements.

Accounts Receivable. Our accounts receivable balance is stated at amortized cost less an allowance determined using the expected credit loss model. In addition, our accounts receivable balance is reduced by certain sales deduction reserves where we have the right of offset with the customer. We generally do not require collateral.

Concentrations of Credit Risk and Credit Losses. Financial instruments that potentially subject us to significant concentrations of credit risk consist primarily of cash equivalents, restricted cash equivalents and accounts receivable. From time to time, we invest our excess cash in high-quality, liquid money market instruments maintained by major banks and financial institutions. We have not experienced any losses on our cash equivalents.

With respect to our accounts receivable, we have no history of significant losses. Approximately 83% and 91% of our gross trade accounts receivable balances represent amounts due from three customers (Cardinal Health, Inc., McKesson Corporation and AmerisourceBergen Corporation) at December 31, 2022 and December 31, 2021, respectively. We perform ongoing credit evaluations of these and our other customers based on information available to us. We consider these and other factors, including changes in the composition and aging of our accounts receivable, in developing our allowance for expected credit losses. The estimated allowance was not material to the Company's Consolidated Financial Statements at December 31, 2022 or December 31, 2021, nor were the changes to the allowance during any of the periods presented.

We do not currently expect our current or future exposures to credit losses to have a significant impact on us. However, our customers' ability to pay us on a timely basis, or at all, could be affected by factors specific to their respective businesses and/or by economic conditions, including those related to the COVID-19 pandemic, the extent of which cannot be fully predicted.

Inventories. Inventories consist of raw materials, work-in-process and finished goods. Inventory that is in excess of the amount expected to be sold within one year is classified as long-term inventory and is recorded in Other assets in the Consolidated Balance Sheets. The Company capitalizes inventory costs associated with certain products prior to regulatory approval and product launch when it is reasonably certain, based on management's judgment of future commercial use and net realizable value, that the pre-launch inventories will be saleable. The determination to capitalize is made on a product-by-product basis. The Company could be required to write down previously capitalized costs related to pre-launch inventories upon a change in such judgment, a denial or delay of approval by regulatory bodies, a delay in commercialization or other potential factors. Our inventories are stated at the lower of cost or net realizable value.

Cost is determined by the first-in, first-out method. It includes materials, direct labor and an allocation of overhead, but excludes certain period charges and unallocated overheads that are charged to expense in the period in which they are incurred. Unallocated overheads can occur as a consequence of abnormally low production or idle facilities.

Net realizable value is determined by the estimated selling prices in the ordinary course of business, less reasonably predictable costs of completion, disposal and transportation. When necessary, we write-down inventories to net realizable value based on forecasted demand and market and regulatory conditions, which may differ from actual results.

Property, Plant and Equipment. Property, plant and equipment is generally stated at cost less accumulated depreciation. Major improvements are capitalized, while routine maintenance and repairs are expensed as incurred. Costs incurred during the construction or development of property, plant and equipment are capitalized as assets under construction. Once an asset has been placed into service, depreciation expense is taken on a straight-line basis over the estimated useful life of the related assets or, in the case of leasehold improvements and finance lease assets, over the shorter of the estimated useful life and the lease term. As of December 31, 2022, the useful lives of our property, plant and equipment range from 1 year to up to 30 years for buildings, 15 years for machinery and equipment, 10 years for computer equipment and software and 10 years for furniture and fixtures. Depreciation expense is not recorded on assets held for sale. Gains and losses on disposals are included in Other income, net in the Consolidated Statements of Operations. As further described below under the heading "Long-Lived Asset Impairment Testing," our property plant and equipment assets are also subject to impairment reviews.

Computer Software. The Company capitalizes certain costs incurred in connection with obtaining or developing internal-use software, including external direct costs of material and services, and payroll costs for employees directly involved with the software development. Capitalized software costs are included in Property, plant and equipment, net in the Consolidated Balance Sheets and depreciated beginning when the software project is substantially complete and the asset is ready for its intended use. Costs incurred during the preliminary project stage and post-implementation stage, as well as maintenance and training costs, are expensed as incurred.

Lease Accounting. Whenever the Company enters into a new arrangement, it must determine, at the inception date, whether the arrangement is or contains a lease. This determination generally depends on whether the arrangement conveys to the Company the right to control the use of an explicitly or implicitly identified asset for a period of time in exchange for consideration. Control of an underlying asset is conveyed to the Company if the Company obtains the rights to direct the use of and to obtain substantially all of the economic benefits from using the underlying asset.

If a lease exists, the Company must then determine the separate lease and nonlease components of the arrangement. Each right to use an underlying asset conveyed by a lease arrangement should generally be considered a separate lease component if it both: (i) can benefit the Company without depending on other resources not readily available to the Company and (ii) does not significantly affect and is not significantly affected by other rights of use conveyed by the lease. Aspects of a lease arrangement that transfer other goods or services to the Company but do not meet the definition of lease components are considered nonlease components. The consideration owed by the Company pursuant to a lease arrangement is generally allocated to each lease and nonlease component for accounting purposes. However, the Company has elected, for all of its leases, to not separate lease and nonlease components. Each lease component is accounted for separately from other lease components, but together with the associated nonlease components.

For each lease, the Company must then determine the lease term, the present value of lease payments and the classification of the lease as either an operating or finance lease.

The lease term is the period of the lease not cancellable by the Company, together with periods covered by: (i) renewal options the Company is reasonably certain to exercise; (ii) termination options the Company is reasonably certain not to exercise; and (iii) renewal or termination options that are controlled by the lessor.

The present value of lease payments is calculated based on:

- Lease payments—Lease payments include fixed and certain variable payments, less lease incentives, together with amounts probable of being owed by the Company under residual value guarantees and, if reasonably certain of being paid, the cost of certain renewal options and early termination penalties set forth in the lease arrangement. Lease payments exclude consideration that is not related to the transfer of goods and services to the Company.
- Discount rate—The discount rate must be determined based on information available to the Company upon the commencement of a lease. Lessees are required to use the rate implicit in the lease whenever such rate is readily available; however, as the implicit rate in the Company's leases is generally not readily determinable, the Company generally uses the hypothetical incremental borrowing rate it would have to pay to borrow an amount equal to the lease payments, on a collateralized basis, over a timeframe similar to the lease term.

In making the determination of whether a lease is an operating lease or a finance lease, the Company considers the lease term in relation to the economic life of the leased asset, the present value of lease payments in relation to the fair value of the leased asset and certain other factors, including the lessee's and lessor's rights, obligations and economic incentives over the term of the lease.

Generally, upon the commencement of a lease, the Company will record a lease liability and a right-of-use asset. However, the Company has elected, for all underlying assets with initial lease terms of twelve months or less (known as short-term leases), to not recognize a lease liability or right-of-use asset. Lease liabilities are initially recorded at lease commencement as the present value of future lease payments. Right-of-use assets are initially recorded at lease commencement as the initial amount of the lease liability, together with the following, if applicable: (i) initial direct costs incurred by the lessee and (ii) lease payments made by the lessor, net of lease incentives received, prior to lease commencement.

Over the lease term, the Company generally increases its lease liabilities using the effective interest method and decreases its lease liabilities for lease payments made. For finance leases, amortization expense and interest expense are recognized separately in the Consolidated Statements of Operations, with amortization expense generally recorded on a straight-line basis over the lease term and interest expense recorded using the effective interest method. For operating leases, a single lease cost is generally recognized in the Consolidated Statements of Operations on a straight-line basis over the lease term unless an impairment has been recorded with respect to a leased asset. Lease costs for short-term leases not recognized in the Consolidated Balance Sheets are recognized in the Consolidated Statements of Operations on a straight-line basis over the lease term. Variable lease costs not initially included in the lease liability and right-of-use asset impairment charges are expensed as incurred. Right-of-use assets are assessed for impairment, similar to other long-lived assets.

Cloud Computing Arrangements. The Company may from time to time incur costs in connection with hosting arrangements that are service contracts. The Company capitalizes any such implementation costs, expenses them over the terms of the respective hosting arrangements and subjects them to impairment testing consistent with other long-lived assets.

Finite-Lived Intangible Assets. Our finite-lived intangible assets consist of license rights and developed technology. Upon acquisition, intangible assets are generally initially recorded at fair value if acquired in a business combination, or at cost if otherwise. There are several methods that can be used to determine fair value. For intangible assets, we typically use an income approach. This approach starts with our forecast of all of the expected future net cash flows. Revenues are estimated based on relevant market size and growth factors, expected industry trends, individual project life cycles and, if applicable, the life of any estimated period of marketing exclusivity, such as that granted by a patent. The pricing, margins and expense levels of similar products are considered if available. For certain licensed assets, our estimates of future cash flows consider periods covered by renewal options to the extent we have the intent and ability, at the date of the estimate, to renew the underlying license agreements. These cash flows are then adjusted to present value by applying an appropriate discount rate that reflects the risk factors associated with the cash flow streams.

To the extent an intangible asset is deemed to have a finite life and to be held and used, it is amortized over its estimated useful life using either the straight-line method or, in the case of certain developed technology assets, an accelerated amortization model. The values of these various assets are subject to continuing scientific, medical and marketplace uncertainty. Factors giving rise to our initial estimate of useful lives are subject to change. Significant changes to any of these factors may result in adjustments to the useful life of the asset and an acceleration of related amortization expense, which could cause our net income and net income per share to decrease. Amortization expense is not recorded on assets held for sale.

As further described under the heading "Long-Lived Asset Impairment Testing," our finite-lived intangible assets are also subject to impairment reviews.

Developed Technology. Our developed technology assets subject to amortization have useful lives ranging from 6 years to 16 years, with a weighted average useful life of approximately 12 years. We determine amortization periods and methods of amortization for developed technology assets based on our assessment of various factors impacting estimated useful lives and the timing and extent of estimated cash flows of the acquired assets, including the strength of the intellectual property protection of the product (if applicable), contractual terms and various other competitive and regulatory issues.

License Rights. Our license rights subject to amortization have useful lives ranging from 7 years to 15 years, with a weighted average useful life of approximately 14 years. We determine amortization periods for licenses based on our assessment of various factors including the expected launch date of the product, the strength of the intellectual property protection of the product (if applicable), contractual terms and various other competitive, developmental and regulatory issues.

Long-Lived Asset Impairment Testing. Long-lived assets, including property, plant and equipment and finite-lived intangible assets, are assessed for impairment whenever events or changes in circumstances indicate the assets may not be recoverable. Recoverability of an asset that will continue to be used in our operations is measured by comparing the carrying amount of the asset to the forecasted undiscounted future cash flows related to the asset. In the event the carrying amount of the asset exceeds its undiscounted future cash flows and the carrying amount is not considered recoverable, impairment may exist. An impairment loss, if any, is measured as the excess of the asset's carrying amount over its fair value, generally based on a discounted future cash flow method, independent appraisals or offers from prospective buyers. An impairment loss would be recognized in the Consolidated Statements of Operations in the period that the impairment occurs.

In the case of long-lived assets to be disposed of by sale or otherwise, including assets held for sale, the assets and the associated liabilities to be disposed of together as a group in a single transaction (the disposal group) are measured at the lower of their carrying amount or fair value less cost to sell. Prior to disposal, losses are recognized for any initial or subsequent write-down to fair value less cost to sell, while gains are recognized for any subsequent increase in fair value less cost to sell, but not in excess of any cumulative losses previously recognized. Any gains or losses not previously recognized that result from the sale of a disposal group shall be recognized at the date of sale.

Acquired in-Process Research and Development Assets. Acquired in-process research and development charges are generally recognized in periods in which in-process research and development assets (with no alternative future use in other research and development projects) are acquired from third parties in connection with an asset acquisition, or when costs are incurred (up to the point of regulatory approval) for upfront or milestone payments to third parties associated with in-process research and development. Otherwise, acquired in-process research and development assets are generally recognized as indefinite-lived intangible assets. Such assets are generally initially recorded at fair value if acquired in a business combination, or at cost if otherwise. Any indefinite-lived intangible assets are not subject to amortization. Instead, they are tested for impairment annually, as of October 1, and when events or changes in circumstances indicate that the asset might be impaired. If the fair value of the intangible assets is less than its carrying amount, an impairment loss is recognized for the difference. Assets that receive regulatory approval are reclassified and accounted for as finite-lived intangible assets.

Goodwill. While amortization expense is not recorded on goodwill, goodwill is subject to impairment reviews. An impairment assessment is conducted as of October 1, or more frequently whenever events or changes in circumstances indicate that the asset might be impaired.

We perform the goodwill impairment test by estimating the fair value of the reporting units using an income approach that utilizes a discounted cash flow model or, where appropriate, a market approach. Any goodwill impairment charge we recognize for a reporting unit is equal to the lesser of: (i) the total goodwill allocated to that reporting unit and (ii) the amount by which that reporting unit's carrying amount exceeds its fair value.

Contingencies. The Company is subject to various patent challenges, product liability claims, government investigations and other legal proceedings in the ordinary course of business. Contingent accruals and legal settlements are recorded in the Consolidated Statements of Operations as Litigation-related and other contingencies, net (or as Discontinued operations, net of tax in the case of vaginal mesh matters) when the Company determines that a loss is both probable and reasonably estimable. Legal fees and other expenses related to litigation are expensed as incurred and are generally included in Selling, general and administrative expenses in the Consolidated Statements of Operations (or as Discontinued operations, net of tax in the case of vaginal mesh matters).

Due to the fact that legal proceedings and other contingencies are inherently unpredictable, our estimates of the probability and amount of any such liabilities involve significant judgment regarding future events.

The Company records receivables from its insurance carriers only when the realization of the potential claim for recovery is considered probable.

Contingent Consideration. Certain of the Company's acquisitions involve the potential for future payment of consideration that is contingent upon the occurrence of a future event, such as: (i) the achievement of specified regulatory, operational and/or commercial milestones or (ii) royalty payments, such as those relating to future product sales. Contingent consideration liabilities related to an asset acquisition are initially recorded when considered probable and reasonably estimable, which may occur subsequent to the acquisition date. Subsequent changes in the recorded amounts are generally recorded as adjustments to the cost of the acquired assets. Contingent consideration liabilities related to a business combination are initially recorded at fair value on the acquisition date using unobservable inputs. These inputs include the estimated amount and timing of projected cash flows, the probability of success (achievement of the contingent event) and the risk-adjusted discount rate used to present value the probability-weighted cash flows. Subsequent to the acquisition date, at each reporting period, the Company remeasures its contingent consideration liabilities to their current estimated fair values, with changes recorded in earnings. Changes to any of the inputs used in determining fair value may result in fair value adjustments that differ significantly from the actual remeasurement adjustments recognized.

Share Repurchases. The Company accounts for the repurchase of ordinary shares, if any, at par value. Under applicable Irish law, ordinary shares repurchased are retired and not displayed separately as treasury stock. Upon retirement of the ordinary shares, the Company records the difference between the weighted average cost of such ordinary shares and the par value of the ordinary shares as an adjustment to Accumulated deficit in the Consolidated Balance Sheets.

Advertising Costs. Advertising costs are expensed as incurred and included in Selling, general and administrative expenses in the Consolidated Statements of Operations. Advertising costs amounted to $130.4 million, $136.8 million and $76.0 million for the years ended December 31, 2022, 2021 and 2020, respectively.

Cost of Revenues. Cost of revenues includes all costs directly related to bringing both purchased and manufactured products to their final selling destination. Amounts include purchasing and receiving costs, direct and indirect costs to manufacture products including direct materials, direct labor and direct overhead expenses necessary to acquire and convert purchased materials and supplies into finished goods, royalties paid or owed by Endo on certain in-licensed products, inspection costs, depreciation of certain property, plant and equipment, amortization of intangible assets, lease costs, warehousing costs, freight charges, costs to operate our equipment and other shipping and handling costs, among others.

Restructuring. Restructuring charges related to nonretirement postemployment benefits that fall under *Accounting Standards Codification Topic 712, Compensation—Nonretirement Postemployment Benefits* are recognized when the severance liability is determined to be probable of being paid and reasonably estimable. One-time benefits related to restructurings, if any, are recognized in accordance with *Accounting Standards Codification Topic 420, Exit or Disposal Cost Obligations* when the programs are approved, the affected employees are identified, the terms of the arrangement are established, it is determined changes to the plan are unlikely to occur and the arrangements are communicated to employees. Other restructuring costs are generally expensed as incurred.

Share-Based Compensation. From time to time, the Company grants share-based compensation awards to certain employees and non-employee directors. Generally, the grant-date fair value of each award is recognized as expense over the requisite service period. However, expense recognition differs in the case of certain PSUs where the ultimate payout is performance-based. For these awards, at each reporting period, the Company generally estimates the ultimate payout and adjusts the cumulative expense based on its estimate and the percent of the requisite service period that has elapsed. Share-based compensation expense is reduced for estimated future forfeitures. These estimates are revised in future periods if actual forfeitures differ from the estimates. Changes in forfeiture estimates impact compensation expense in the period in which the change in estimate occurs. New ordinary shares are generally issued upon the exercise of stock options or vesting of stock awards by employees and non-employee directors. Refer to Note 19. Share-based Compensation for additional discussion.

Foreign Currency. The Company operates in various jurisdictions both inside and outside of the U.S. While the Company's reporting currency is the U.S. dollar, the Company has concluded that certain of its distinct and separable operations have functional currencies other than the U.S. dollar. Further, certain of the Company's operations hold assets and liabilities and recognize income and expenses denominated in various local currencies, which may differ from their functional currencies.

Assets and liabilities are first remeasured from local currency to functional currency, generally using end-of-period exchange rates. Foreign currency income and expenses are generally remeasured using average exchange rates in effect during the year. In the case of nonmonetary assets and liabilities such as inventories, prepaid expenses, property, plant and equipment, goodwill and other intangible assets, and related income statement amounts, such as depreciation expense, historical exchange rates are used for remeasurement. The net effect of remeasurement is included in Other income, net in the Consolidated Statements of Operations.

As part of the Company's consolidation process, assets and liabilities of entities with functional currencies other than the U.S. dollar are translated into U.S. dollars at end-of-period exchange rates. Income and expenses are translated using average exchange rates in effect during the year. The net effect of translation, as well as any foreign currency gains or losses on intercompany transactions considered to be of a long-term investment nature, are recognized as foreign currency translation, a component of Other comprehensive (loss) income. Upon the sale or liquidation of an investment in a foreign operation, the Company records a reclassification adjustment out of Other comprehensive (loss) income for the corresponding accumulated amount of foreign currency translation gain or loss.

Income Taxes. The Company accounts for income taxes under the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements. Under this method, deferred tax assets and liabilities are determined based on the differences between the financial statement and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. The effect of a change in tax rates on deferred tax assets and liabilities is recognized in income in the period that includes the enactment date. The Company records net deferred tax assets to the extent it believes these assets will more likely than not be realized. In making such a determination, the Company considers all available positive and negative evidence, including projected future taxable income, tax-planning strategies and results of recent operations. In the event that the Company were to determine that it would be able to realize its deferred tax assets in the future in excess of their net recorded amount, the Company would make an adjustment to the deferred tax asset valuation allowance, which would reduce the provision for income tax.

The Company records unrecognized income tax positions (UTPs) on the basis of a two-step process whereby the Company first determines whether it is more likely than not that the tax positions will be sustained based on the technical merits of the position and then measures those tax positions that meet the more-likely-than-not recognition threshold. The Company recognizes the largest amount of tax benefit that is greater than 50% likely to be realized upon ultimate settlement with the tax authority. The Company generally recognizes changes in UTPs, interest and penalties in the Income tax expense line in the Consolidated Statements of Operations. Refer to Note 21. Income Taxes for information about the classification of liabilities related to UTPs, including interest and penalties, in the Consolidated Balance Sheets.

Comprehensive Income. Comprehensive income or loss includes all changes in equity during a period except those that resulted from investments by or distributions to a company's shareholders. Other comprehensive income or loss refers to revenues, expenses, gains and losses that are included in comprehensive income, but excluded from net income as these amounts are recorded directly as an adjustment to shareholders' equity.

Government Assistance Transactions. Our PSP LLC subsidiary is party to the U.S. Government Agreement. Under the terms of the U.S. Government Agreement, our Rochester facility will establish new sterile fill-finish manufacturing assets capable of processing liquid or lyophilized products requiring Biosafety Level (BSL) 2 containment in order to establish and sustain BSL 2 sterile fill-finish production capacity to create and maintain industrial base capabilities for the national defense.

The Company has concluded that reimbursements it receives pursuant to the U.S. Government Agreement, which are further described below, are not within the scope of *Accounting Standards Codification Topic 606, Revenue from Contracts with Customers* (ASC 606) because the U.S. government does not meet the definition of a "customer" as defined by ASC 606. We are instead accounting for the U.S. Government Agreement under other guidance including, for elements of the contract for which there is no authoritative guidance under U.S. GAAP, by applying the relevant accounting principles contained in *International Accounting Standards 20—Accounting for Government Grants and Disclosure of Government Assistance* by analogy.

Under this model, reimbursements we receive from the U.S. government for qualifying capital expenditures meet the definition of grants related to assets as the primary purpose for the reimbursements is to fund the purchase and construction of capital assets to increase production capacity. We recognize these reimbursements as deferred income in the Consolidated Balance Sheets as either Accounts payable and accrued expenses (for any current portion) or Other liabilities (for any noncurrent portion) when there is reasonable assurance the conditions of the grant will be met and the grant will be received. Refer to Note 16. Commitments and Contingencies for additional discussion of this agreement.

NOTE 4. DISCONTINUED OPERATIONS AND ASSET SALES

Astora

The operating results of the Company's Astora business, which the Board resolved to wind down in 2016, are reported as Discontinued operations, net of tax in the Consolidated Statements of Operations for all periods presented. The following table provides the operating results of Astora Discontinued operations, net of tax, for the years ended December 31, 2022, 2021 and 2020 (in thousands):

	2022	2021	2020
Litigation-related and other contingencies, net	$ —	$ 25,000	$ 41,097
Loss from discontinued operations before income taxes	$ (15,543)	$ (49,594)	$ (67,847)
Income tax benefit	$ (2,056)	$ (5,430)	$ (4,327)
Discontinued operations, net of tax	$ (13,487)	$ (44,164)	$ (63,520)

Loss from discontinued operations before income taxes includes Litigation-related and other contingencies, net, mesh-related legal defense costs and certain other items.

The cash flows from discontinued operating activities related to Astora included the impact of net losses of $13.5 million, $44.2 million and $63.5 million for the years ended December 31, 2022, 2021 and 2020, respectively, and the impact of cash activity related to vaginal mesh cases. During the periods presented above, there were no material net cash flows related to Astora discontinued investing activities and there was no depreciation or amortization expense related to Astora.

Certain Assets and Liabilities of Endo's Retail Generics Business

In November 2020, we announced the initiation of several strategic actions to further optimize the Company's operations and increase overall efficiency (the 2020 Restructuring Initiative), which are further discussed in Note 5. Restructuring. These actions include an initiative to exit certain of our manufacturing and other sites to optimize our retail generics business cost structure.

Certain of these sites and certain corresponding assets and liabilities were sold in 2021 to subsidiaries of Strides Pharma Science Limited and certain other entities. The assets sold included certain of our manufacturing facilities and related fixed assets in Chestnut Ridge, New York and Irvine, California, as well as certain U.S. retail generics products and certain related product inventory. As a result of these sales, we became entitled to aggregate cash consideration of approximately $25.6 million, substantially all of which was received by December 31, 2021, as well as certain non-cash consideration of approximately $5.8 million. In connection with these sales, we recognized the following amounts in 2021: (i) a pre-tax disposal loss of $42.2 million to write down the carrying amount of the disposal group to fair value, less cost to sell, which we recorded in Asset impairment charges in the Consolidated Statements of Operations, and (ii) a pre-tax net reversal of $25.4 million of expense, primarily related to avoided severance costs for employees that transitioned to the purchasers in connection with these 2021 sales.

In 2022, we entered into a definitive agreement to sell certain additional assets located in Chestnut Ridge, New York to Ram Ridge Partners BH LLC. The assets primarily consisted of property, plant and equipment. In October 2022, the Bankruptcy Court approved the sale of the assets. The sale closed during the fourth quarter of 2022. As a result of this sale, we became entitled to aggregate cash consideration of approximately $18.5 million, substantially all of which was received by December 31, 2022. In connection with this sale, we recognized a pre-tax disposal gain of approximately $8.4 million in 2022, which we recorded in Other income, net in the Consolidated Statements of Operations.

The assets described in this section, which primarily related to the Company's Generic Pharmaceuticals segment, did not meet the requirements for treatment as a discontinued operation. The amounts described in this section that were recognized in our Consolidated Statements of Operations are included in the quantitative disclosures of the 2020 Restructuring Initiative included in Note 5. Restructuring.

NOTE 5. RESTRUCTURING

2020 Restructuring Initiative

As noted above, in November 2020, the Company announced the initiation of several strategic actions to further optimize the Company's operations and increase overall efficiency. These actions were initiated with the expectation of, among other things, generating significant cost savings to be reinvested, among other things, to support the Company's key strategic priority to expand and enhance its product portfolio. These actions included the following:

- Optimizing the Company's retail generics business cost structure by exiting manufacturing and other sites in Irvine, California, Chestnut Ridge, New York and India.
- Improving operating flexibility and reducing general and administrative costs by transferring certain transaction processing activities to third-party global business process service providers.
- Increasing organizational effectiveness by further integrating the Company's commercial, operations and research and development functions, respectively, to support the Company's key strategic priorities.

As a result of the 2020 Restructuring Initiative, the Company's global workforce was reduced by approximately 300 net full-time positions. The Company expects to realize annualized pre-tax cash savings (without giving effect to the costs described below) of approximately $85 million to $95 million by the first half of 2023, primarily related to reductions in Cost of revenues of approximately $65 million to $70 million and other expenses, including Selling, general and administrative and Research and development expenses, of approximately $20 million to $25 million. Future costs associated with the 2020 Restructuring Initiative are not expected to be material.

The following pre-tax net amounts related to the 2020 Restructuring Initiative are included in the Company's Consolidated Statements of Operations during the years ended December 31, 2022, 2021 and 2020 (in thousands):

	2022	2021	2020
Net restructuring charges (charge reversals) related to:			
Accelerated depreciation	$ 3,773	$ 24,718	$ 22,459
Asset impairments	—	42,155	7,391
Inventory adjustments	1,494	6,968	3,097
Employee separation, continuity and other benefit-related costs	1,216	(7,384)	60,025
Certain other restructuring costs	795	2,012	664
Total	$ 7,278	$ 68,469	$ 93,636

These pre-tax net amounts were primarily attributable to our Generic Pharmaceuticals segment, which incurred $5.4 million, $49.9 million and $79.0 million of pre-tax net charges during the years ended December 31, 2022, 2021 and 2020, respectively. The remaining amounts related to our other segments and certain corporate unallocated costs.

As of December 31, 2022, cumulative amounts incurred to date include charges related to accelerated depreciation of approximately $51.0 million, asset impairments related to certain identifiable intangible assets, operating lease assets and disposal groups totaling approximately $49.5 million, inventory adjustments of approximately $11.6 million, employee separation, continuity and other benefit-related costs, net of approximately $53.9 million and certain other restructuring costs of approximately $3.5 million. Of these amounts, approximately $134.3 million was attributable to the Generic Pharmaceuticals segment, with the remaining amounts relating to our other segments and certain corporate unallocated costs.

The following pre-tax net amounts related to the 2020 Restructuring Initiative are included in the Company's Consolidated Statements of Operations during the years ended December 31, 2022, 2021 and 2020 (in thousands):

	2022	2021	2020
Net restructuring charges (charge reversals) included in:			
Cost of revenues	$ 3,966	$ 6,244	$ 53,297
Selling, general and administrative	208	20,788	27,857
Research and development	3,104	1,367	5,091
Asset impairment charges	—	42,155	7,391
Other income, net	—	(2,085)	—
Total	$ 7,278	$ 68,469	$ 93,636

In addition to the pre-tax net amounts summarized above, as part of the 2020 Restructuring Initiative, we recognized a pre-tax disposal gain of approximately $8.4 million during the fourth quarter of 2022 as a result of the Chestnut Ridge, New York sale transaction, which is further described in Note 4. Discontinued Operations and Asset Sales. The assets sold primarily related to our Generic Pharmaceuticals segment.

Changes to the liability for the 2020 Restructuring Initiative during the years ended December 31, 2022, 2021 and 2020 were as follows (in thousands):

	Employee Separation, Continuity and Other Benefit-Related Costs	Certain Other Restructuring Costs	Total
Liability balance as of December 31, 2019	$ —	$ —	$ —
Net charges	60,025	664	60,689
Cash payments	(1,687)	—	(1,687)
Liability balance as of December 31, 2020	$ 58,338	$ 664	$ 59,002
Net (charge reversals) charges	(7,384)	3,711	(3,673)
Cash payments	(39,975)	(4,170)	(44,145)
Liability balance as of December 31, 2021	$ 10,979	$ 205	$ 11,184
Net charges	1,216	796	2,012
Cash payments	(11,926)	(1,001)	(12,927)
Liability balance as of December 31, 2022	$ 269	$ —	$ 269

2022 Restructuring Initiative

In April 2022, the Company communicated the initiation of actions to streamline and simplify certain functions, including its commercial organization, to increase its overall organizational effectiveness and better align with current and future needs. In December 2022, the Company announced it would be taking certain additional actions to cease the production and sale of QWO® in light of market concerns about the extent and variability of bruising following initial treatment as well as the potential for prolonged skin discoloration. These actions, which are collectively referred to herein as the 2022 Restructuring Initiative, were initiated with the expectation of, among other things, generating cost savings, with a portion to be reinvested to support the Company's key strategic priority to expand and enhance its product portfolio. In December 2022, the Bankruptcy Court approved an order authorizing the Company to cease the production and commercialization of QWO® and granting related relief.

As a result of the 2022 Restructuring Initiative, the Company's global workforce is ultimately expected to be reduced by up to approximately 190 net full-time positions. The Company expects to realize annualized pre-tax cash savings (without giving effect to the costs described below) of approximately $105 million to $125 million by the end of 2023, primarily related to reductions in Selling, general and administrative expenses and Cost of revenues. Future costs associated with the 2022 Restructuring Initiative are not expected to be material.

The following pre-tax net amounts related to the 2022 Restructuring Initiative are included in the Company's Consolidated Statements of Operations during the year ended December 31, 2022 (in thousands):

	2022
Net restructuring charges related to:	
Asset impairments	$ 180,248
Inventory adjustments	34,870
Employee separation, continuity and other benefit-related costs	28,345
Certain other restructuring costs	8,656
Total	$ 252,119

These pre-tax net amounts were primarily attributable to our Branded Pharmaceuticals segment, which incurred $238.6 million of pre-tax net charges during the year ended December 31, 2022. The remaining amounts related to our Generic Pharmaceuticals segment and certain corporate unallocated costs.

The following pre-tax net amounts related to the 2022 Restructuring Initiative are included in the Company's Consolidated Statements of Operations during the year ended December 31, 2022 (in thousands):

	2022
Net restructuring charges included in:	
Cost of revenues	$ 49,078
Selling, general and administrative	18,692
Research and development	4,101
Asset impairment charges	180,248
Total	$ 252,119

Changes to the liability for the 2022 Restructuring Initiative during the year ended December 31, 2022 were as follows (in thousands):

	Employee Separation, Continuity and Other Benefit-Related Costs	Certain Other Restructuring Costs	Total
Liability balance as of December 31, 2021	$ —	$ —	$ —
Net charges	28,345	1,102	29,447
Cash payments	(13,348)	(1,102)	(14,450)
Liability balance as of December 31, 2022	$ 14,997	$ —	$ 14,997

The liability at December 31, 2022 is classified as current and is included in Accounts payable and accrued expenses in the Consolidated Balance Sheets.

NOTE 6. SEGMENT RESULTS

The Company's four reportable business segments are Branded Pharmaceuticals, Sterile Injectables, Generic Pharmaceuticals and International Pharmaceuticals. These segments reflect the level at which the chief operating decision maker regularly reviews financial information to assess performance and to make decisions about resources to be allocated. Each segment derives revenue from the sales or licensing of its respective products and is discussed in more detail below.

We evaluate segment performance based on Segment adjusted income from continuing operations before income tax, which we define as Loss from continuing operations before income tax and before acquired in-process research and development charges; acquisition-related and integration items, including transaction costs and changes in the fair value of contingent consideration; cost reduction and integration-related initiatives such as separation benefits, continuity payments, other exit costs and certain costs associated with integrating an acquired company's operations; certain amounts related to strategic review initiatives; asset impairment charges; amortization of intangible assets; inventory step-up recorded as part of our acquisitions; litigation-related and other contingent matters; certain legal costs; gains or losses from early termination of debt; debt modification costs; gains or losses from the sales of businesses and other assets; foreign currency gains or losses on intercompany financing arrangements; reorganization items, net; and certain other items.

Certain corporate expenses incurred by the Company are not directly attributable to any specific segment. Accordingly, these costs are not allocated to any of the Company's segments and are included in the results below as "Corporate unallocated costs." Interest income and expense are also considered corporate items and not allocated to any of the Company's segments. The Company's Total segment adjusted income from continuing operations before income tax is equal to the combined results of each of its segments.

Branded Pharmaceuticals

Our Branded Pharmaceuticals segment includes a variety of branded products in the areas of urology, orthopedics, endocrinology and bariatrics, among others. Products in this segment include XIAFLEX®, SUPPRELIN® LA, AVEED®, NASCOBAL® Nasal Spray, PERCOCET®, TESTOPEL® and EDEX®, among others.

Sterile Injectables

Our Sterile Injectables segment consists primarily of branded sterile injectable products such as VASOSTRICT®, ADRENALIN® and APLISOL®, among others, and certain generic sterile injectable products, including ertapenem for injection (the authorized generic of Merck's Invanz®) and ephedrine sulfate injection, among others.

Generic Pharmaceuticals

Our Generic Pharmaceuticals segment consists of a product portfolio including solid oral extended-release products, solid oral immediate-release products, liquids, semi-solids, patches, powders, ophthalmics and sprays and includes products that treat and manage a wide variety of medical conditions.

International Pharmaceuticals

Our International Pharmaceuticals segment includes a variety of specialty pharmaceutical products, including OTC products, sold outside the U.S., primarily in Canada through our operating company Paladin.

The following represents selected information for the Company's reportable segments for the years ended December 31, 2022, 2021 and 2020 (in thousands):

	2022	2021	2020
Net revenues from external customers:			
Branded Pharmaceuticals	$ 851,142	$ 893,617	$ 781,780
Sterile Injectables	589,633	1,266,097	1,238,847
Generic Pharmaceuticals	795,457	740,586	783,110
International Pharmaceuticals (1)	82,643	92,906	99,337
Total net revenues from external customers	$ 2,318,875	$ 2,993,206	$ 2,903,074
Segment adjusted income from continuing operations before income tax:			
Branded Pharmaceuticals	$ 366,554	$ 384,186	$ 377,526
Sterile Injectables	349,424	998,453	950,145
Generic Pharmaceuticals	336,133	160,046	87,178
International Pharmaceuticals	19,920	30,325	41,022
Total segment adjusted income from continuing operations before income tax	$ 1,072,031	$ 1,573,010	$ 1,455,871

(1) Revenues generated by our International Pharmaceuticals segment are primarily attributable to external customers located in Canada

There were no material revenues from external customers attributed to an individual country outside of the U.S. during any of the periods presented.

The table below provides reconciliations of our Total consolidated loss from continuing operations before income tax, which is determined in accordance with U.S. GAAP, to our Total segment adjusted income from continuing operations before income tax for the years ended December 31, 2022, 2021 and 2020 (in thousands):

	2022	2021	2020
Total consolidated loss from continuing operations before income tax	$ (2,888,102)	$ (546,603)	$ (26,518)
Interest expense, net	349,776	562,353	532,939
Corporate unallocated costs (1)	182,335	180,866	157,723
Amortization of intangible assets	337,311	372,907	427,543
Acquired in-process research and development charges	68,700	25,120	33,329
Amounts related to continuity and separation benefits, cost reductions and strategic review initiatives (2)	198,381	90,912	126,282
Certain litigation-related and other contingencies, net (3)	478,722	345,495	(19,049)
Certain legal costs (4)	31,756	136,148	67,819
Asset impairment charges (5)	2,142,746	414,977	120,344
Acquisition-related and integration items, net (6)	408	(8,379)	16,549
Loss on extinguishment of debt	—	13,753	—
Foreign currency impact related to the remeasurement of intercompany debt instruments	(5,328)	797	1,919
Reorganization items, net (7)	202,978	—	—
Other, net (8)	(27,652)	(15,336)	16,991
Total segment adjusted income from continuing operations before income tax	$ 1,072,031	$ 1,573,010	$ 1,455,871

(1) Amounts include certain corporate overhead costs, such as headcount, facility and corporate litigation expenses and certain other income and expenses

(2) Amounts in 2022 include net employee separation, continuity and other benefit-related charges of $85 6 million, accelerated depreciation charges of $3 8 million, inventory charges related to restructurings of $36 4 million and other net charges, including those related to strategic review initiatives, of $72 7 million Amounts in 2021 include net employee separation, continuity and other benefit-related charges of $8 8 million, accelerated depreciation charges of $24 7 million and other net charges, including those related to strategic review initiatives, of $57 4 million Amounts in 2020 include net employee separation, continuity and other benefit-related charges of $86 9 million, accelerated depreciation charges of $22 5 million and other net charges, including those related to strategic review initiatives, of $16 9 million These amounts relate primarily to our restructuring activities as further described in Note 5 Restructuring, certain continuity and transitional compensation arrangements, certain other cost reduction initiatives and certain strategic review initiatives, including costs incurred in connection with our bankruptcy proceedings, which are included in this row until the Petition Date and in the Reorganization items, net row thereafter

(3) Amounts include adjustments to our accruals for litigation-related settlement charges Our material legal proceedings and other contingent matters are described in more detail in Note 16 Commitments and Contingencies

(4) Amounts relate to opioid-related legal expenses The amount in 2022 reflects the recovery of certain previously-incurred opioid-related legal expenses

(5) Amounts primarily relate to charges to impair goodwill and intangible assets, property, plant and equipment, operating lease right-of-use assets and certain disposal group assets For additional information, refer to Note 4 Discontinued Operations and Asset Sales, Note 5 Restructuring, Note 7 Fair Value Measurements, Note 9 Leases, Note 10 Property, Plant and Equipment and Note 11 Goodwill and Other Intangibles

(6) Amounts primarily relate to changes in the fair value of contingent consideration

(7) Amounts relate to the net expense or income recognized during our bankruptcy proceedings required to be presented as Reorganization items, net under ASC 852 Refer to Note 2 Bankruptcy Proceedings for further details

(8) Amounts in 2021 include gains of $15 5 million associated with the termination of certain contracts, partially offset by $3 9 million of third-party fees incurred in connection with the March 2021 Refinancing Transactions, which were accounted for as debt modification costs as further discussed in Note 15 Debt Amounts in 2020 include $31 1 million of third-party fees incurred in connection with the June 2020 Refinancing Transactions (as defined below), which were accounted for as debt modification costs as further discussed in Note 15 Debt Other amounts in this row relate to gains and losses on sales of businesses and other assets and certain other items

Asset information is not reviewed or included within our internal management reporting. Therefore, the Company has not disclosed asset information for each reportable segment.

During the years ended December 31, 2022, 2021 and 2020, the Company disaggregated its revenue from contracts with customers into the categories included in the table below (in thousands). The Company believes these categories depict how the nature, timing and uncertainty of revenue and cash flows are affected by economic factors.

	2022	2021	2020
Branded Pharmaceuticals:			
Specialty Products:			
XIAFLEX®	$ 438,680	$ 432,344	$ 316,234
SUPPRELIN® LA	113,011	114,374	88,182
Other Specialty (1)	70,009	86,432	92,662
Total Specialty Products	$ 621,700	$ 633,150	$ 497,078
Established Products:			
PERCOCET®	$ 103,943	$ 103,788	$ 110,112
TESTOPEL®	38,727	43,636	35,234
Other Established (2)	86,772	113,043	139,356
Total Established Products	$ 229,442	$ 260,467	$ 284,702
Total Branded Pharmaceuticals (3)	$ 851,142	$ 893,617	$ 781,780
Sterile Injectables:			
VASOSTRICT®	$ 253,696	$ 901,735	$ 785,646
ADRENALIN®	114,304	124,630	152,074
Other Sterile Injectables (4)	221,633	239,732	301,127
Total Sterile Injectables (3)	$ 589,633	$ 1,266,097	$ 1,238,847
Total Generic Pharmaceuticals (5)	$ 795,457	$ 740,586	$ 783,110
Total International Pharmaceuticals (6)	$ 82,643	$ 92,906	$ 99,337
Total revenues, net	$ 2,318,875	$ 2,993,206	$ 2,903,074

(1) Products included within Other Specialty include AVEED®, NASCOBAL® Nasal Spray and QWO®
(2) Products included within Other Established include, but are not limited to, EDEX®
(3) Individual products presented above represent the top two performing products in each product category for the year ended December 31, 2022 and/or any product having revenues in excess of $25 million during any completed quarterly period in 2022 or 2021
(4) Products included within Other Sterile Injectables include APLISOL®, ertapenem for injection and others
(5) The Generic Pharmaceuticals segment is comprised of a portfolio of products that are generic versions of branded products, are distributed primarily through the same wholesalers, generally have limited or no intellectual property protection and are sold within the U S During 2022, varenicline tablets (Endo's generic version of Pfizer Inc 's Chantix®), which launched in September 2021, made up 13% of consolidated total revenues No other individual product within this segment has exceeded 5% of consolidated total revenues for the periods presented
(6) The International Pharmaceuticals segment, which accounted for less than 5% of consolidated total revenues for each of the periods presented, includes a variety of specialty pharmaceutical products sold outside the U S , primarily in Canada through Endo's operating company Paladin

The following represents depreciation expense for our reportable segments for the years ended December 31, 2022, 2021 and 2020 (in thousands):

	2022	2021	2020
Branded Pharmaceuticals	$ 9,862	$ 10,632	$ 11,758
Sterile Injectables	20,224	17,796	17,400
Generic Pharmaceuticals	16,952	47,343	52,614
International Pharmaceuticals	3,638	4,242	4,530
Corporate unallocated	3,642	4,178	4,962
Total depreciation expense	$ 54,318	$ 84,191	$ 91,264

NOTE 7. FAIR VALUE MEASUREMENTS

Fair value guidance establishes a three-tier fair value hierarchy, which prioritizes the inputs used in measuring fair value. These tiers include:

- Level 1—Quoted prices in active markets for identical assets or liabilities.
- Level 2—Inputs other than Level 1 that are observable, either directly or indirectly, such as quoted prices for similar assets or liabilities; quoted prices in markets that are not active; or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.
- Level 3—Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

Financial Instruments

The financial instruments recorded in our Consolidated Balance Sheets include cash and cash equivalents, restricted cash and cash equivalents, accounts receivable, accounts payable and accrued expenses, acquisition-related contingent consideration and debt obligations. Included in cash and cash equivalents and restricted cash and cash equivalents are money market funds representing a type of mutual fund required by law to invest in low-risk securities (for example, U.S. government bonds, U.S. Treasury Bills and commercial paper). Money market funds pay dividends that generally reflect short-term interest rates. Due to their initial maturities, the carrying amounts of non-restricted and restricted cash and cash equivalents (including money market funds), accounts receivable, accounts payable and accrued expenses approximate their fair values.

Restricted Cash and Cash Equivalents

The following table presents current and noncurrent restricted cash and cash equivalent balances at December 31, 2022 and December 31, 2021 (in thousands):

	Balance Sheet Line Items	December 31, 2022	December 31, 2021
Restricted cash and cash equivalents—current (1)	Restricted cash and cash equivalents	$ 145,358	$ 124,114
Restricted cash and cash equivalents—noncurrent (2)	Other assets	85,000	—
Total restricted cash and cash equivalents		$ 230,358	$ 124,114

(1) Amounts at December 31, 2022 and December 31, 2021 include: (i) restricted cash and cash equivalents associated with litigation-related matters, including $50 7 million and $78 4 million, respectively, held in Qualified Settlement Funds (QSFs) for mesh- and/or opioid-related matters, and (ii) approximately $86 0 million and $45 0 million, respectively, of restricted cash and cash equivalents related to certain insurance-related matters See Note 16 Commitments and Contingencies for further information about litigation-related matters

(2) The amount at December 31, 2022 relates to the TLC Agreement See Note 12 License, Collaboration and Asset Acquisition Agreements for further information about this amount

Acquisition-Related Contingent Consideration

The fair value of contingent consideration liabilities is determined using unobservable inputs; hence, these instruments represent Level 3 measurements within the above-defined fair value hierarchy. These inputs include the estimated amount and timing of projected cash flows, the probability of success (achievement of the contingent event) and the risk-adjusted discount rate used to present value the probability-weighted cash flows. Subsequent to the acquisition date, at each reporting period, the contingent consideration liability is remeasured at current fair value with changes recorded in earnings. The estimates of fair value are uncertain and changes in any of the estimated inputs used as of the date of this report could have resulted in significant adjustments to fair value. See the “Recurring Fair Value Measurements” section below for additional information on acquisition-related contingent consideration.

Recurring Fair Value Measurements

The Company's financial assets and liabilities measured at fair value on a recurring basis at December 31, 2022 and December 31, 2021 were as follows (in thousands):

	Fair Value Measurements at December 31, 2022 using:			
	Level 1 Inputs	Level 2 Inputs	Level 3 Inputs	Total
Assets:				
Money market funds (1)	$ 12,226	$ —	$ —	$ 12,226
Liabilities:				
Acquisition-related contingent consideration (2)	$ —	$ —	$ 16,571	$ 16,571

	Fair Value Measurements at December 31, 2021 using:			
	Level 1 Inputs	Level 2 Inputs	Level 3 Inputs	Total
Assets:				
Money market funds (1)	$ 134,847	$ —	$ —	$ 134,847
Liabilities:				
Acquisition-related contingent consideration (2)	$ —	$ —	$ 20,076	$ 20,076

(1) At December 31, 2022 and December 31, 2021, money market funds include $12 2 million and $16 2 million, respectively, in QSFs Amounts in QSFs are considered restricted cash equivalents See Note 16 Commitments and Contingencies for further discussion of our litigation At December 31, 2022 and December 31, 2021, the differences between the amortized cost and the fair value of our money market funds were not material, individually or in the aggregate

(2) At December 31, 2022, the balance of the Company's liability for acquisition-related contingent consideration, which is governed by executory contracts and recorded at the expected amount of the total allowed claim, is classified within Liabilities subject to compromise in the Consolidated Balance Sheets At December 31, 2021, this amount is classified in the Consolidated Balance Sheets as follows: $5 7 million is classified as a current liability and included within Accounts payable and accrued expenses and $14 3 million is classified as a noncurrent liability and included within Other liabilities

Fair Value Measurements Using Significant Unobservable Inputs

The following table presents changes to the Company's liability for acquisition-related contingent consideration, which is measured at fair value on a recurring basis using significant unobservable inputs (Level 3), for the years ended December 31, 2022 and 2021 (in thousands):

	2022	2021
Beginning of period	$ 20,076	$ 36,249
Amounts settled	(3,127)	(7,449)
Changes in fair value recorded in earnings	408	(8,793)
Effect of currency translation	(786)	69
End of period (1)	$ 16,571	$ 20,076

(1) At December 31, 2022, the balance of the Company's liability for acquisition-related contingent consideration, which is governed by executory contracts and recorded at the expected amount of the total allowed claim, is classified within Liabilities subject to compromise in the Consolidated Balance Sheets

At December 31, 2022, the fair value measurements of the contingent consideration obligations were determined using risk-adjusted discount rates ranging from 10.0% to 15.0% (weighted average rate of approximately 10.7%, weighted based on relative fair value). Changes in fair value recorded in earnings related to acquisition-related contingent consideration are included in our Consolidated Statements of Operations as Acquisition-related and integration items, net.

The following table presents changes to the Company's liability for acquisition-related contingent consideration during the year ended December 31, 2022 by acquisition (in thousands):

	Balance as of December 31, 2021	Changes in Fair Value Recorded in Earnings	Amounts Settled and Other	Balance as of December 31, 2022 (1)
Auxilium acquisition	$ 9,038	$ 2,116	$ (536)	$ 10,618
Lehigh Valley Technologies, Inc. acquisitions	3,600	(635)	(665)	2,300
Other	7,438	(1,073)	(2,712)	3,653
Total	$ 20,076	$ 408	$ (3,913)	$ 16,571

(1) At December 31, 2022, the balance of the Company's liability for acquisition-related contingent consideration, which is governed by executory contracts and recorded at the expected amount of the total allowed claim, is classified within Liabilities subject to compromise in the Consolidated Balance Sheets

The following table presents changes to the Company's liability for acquisition-related contingent consideration during the year ended December 31, 2021 by acquisition (in thousands):

	Balance as of December 31, 2020	Changes in Fair Value Recorded in Earnings	Amounts Settled and Other	Balance as of December 31, 2021
Auxilium acquisition	$ 14,484	$ (3,471)	$ (1,975)	$ 9,038
Lehigh Valley Technologies, Inc. acquisitions	13,100	(6,061)	(3,439)	3,600
Other	8,665	739	(1,966)	7,438
Total	$ 36,249	$ (8,793)	$ (7,380)	$ 20,076

Nonrecurring Fair Value Measurements

The Company's financial assets and liabilities measured at fair value on a nonrecurring basis during the years ended December 31, 2022 and 2021 were as follows (in thousands):

	Fair Value Measurements during the Year Ended December 31, 2022 (1) using:			Total Expense for the Year Ended December 31, 2022
	Level 1 Inputs	Level 2 Inputs	Level 3 Inputs	
Intangible assets, excluding goodwill (2)(3)	$ —	$ —	$ 67,082	$ (288,701)
Certain property, plant and equipment	—	—	—	(9,045)
Total	$ —	$ —	$ 67,082	$ (297,746)

	Fair Value Measurements during the Year Ended December 31, 2021 (1) using:			Total Expense for the Year Ended December 31, 2021
	Level 1 Inputs	Level 2 Inputs	Level 3 Inputs	
Intangible assets, excluding goodwill (2)(3)	$ —	$ —	$ 5,011	$ (7,811)
Certain property, plant and equipment	—	—	—	(2,011)
Total	$ —	$ —	$ 5,011	$ (9,822)

(1) The fair value amounts are presented as of the date of the fair value measurement as these assets are not measured at fair value on a recurring basis Such measurements generally occur in connection with our quarter-end financial reporting close procedures

(2) For 2022, these fair value measurements were determined using risk-adjusted discount rates ranging from 9 5% to 12 0% (weighted average rate of approximately 11 8%, weighted based on relative fair value) For 2021, these fair value measurements were determined using risk-adjusted discount rates ranging from 10 0% to 12 0% (weighted average rate of approximately 11 1%, weighted based on relative fair value)

(3) The Company also performed fair value measurements in connection with its goodwill impairment tests Refer to Note 11 Goodwill and Other Intangibles for additional information on goodwill and other intangible asset impairment tests, including information about the valuation methodologies used

NOTE 8. INVENTORIES

Inventories consisted of the following at December 31, 2022 and December 31, 2021 (in thousands):

	December 31, 2022	December 31, 2021
Raw materials (1)	$ 105,975	$ 90,453
Work-in-process (1)	43,057	82,728
Finished goods (1)	125,467	110,371
Total	$ 274,499	$ 283,552

(1) The components of inventory shown in the table above are net of allowances

Inventory in excess of the amount expected to be sold within one year is classified as noncurrent inventory and is not included in the table above. At December 31, 2022 and December 31, 2021, $23.0 million and $10.7 million, respectively, of noncurrent inventory was included in Other assets in the Consolidated Balance Sheets. As of December 31, 2022 and December 31, 2021, the Company's Consolidated Balance Sheets included approximately $5.8 million and $12.2 million, respectively, of capitalized pre-launch inventories related to products that were not yet available to be sold.

NOTE 9. LEASES

We have entered into contracts with third parties to lease a variety of assets, including certain real estate, machinery, equipment, automobiles and other assets.

Our leases frequently allow for lease payments that could vary based on factors such as inflation or the degree of utilization of the underlying asset and the incurrence of contractual charges such as those for common area maintenance or utilities.

Renewal and/or early termination options are common in our lease arrangements, particularly with respect to our real estate leases. Our right-of-use assets and lease liabilities generally exclude periods covered by renewal options and include periods covered by early termination options (based on our conclusion that it is not reasonably certain that we will exercise such options).

Our most significant lease is for our Malvern, Pennsylvania location. The initial term of the lease is through 2024 and includes three renewal options, each for an additional 60-month period. These renewal options are not considered reasonably certain of exercise and are therefore excluded from the right-of-use asset and lease liability.

We are party to certain sublease arrangements, primarily related to our real estate leases, where we act as the lessee and intermediate lessor. For example, we sublease portions of our Malvern, Pennsylvania facility to multiple tenants through sublease arrangements ending in 2024, with certain limited renewal and early termination options.

The following table presents information about the Company's right-of-use assets and lease liabilities at December 31, 2022 and December 31, 2021 (in thousands):

	Balance Sheet Line Items	December 31, 2022	December 31, 2021
Right-of-use assets:			
Operating lease right-of-use assets	Operating lease assets	$ 28,070	$ 34,832
Finance lease right-of-use assets	Property, plant and equipment, net	26,761	38,365
Total right-of-use assets		$ 54,831	$ 73,197
Operating lease liabilities (1):			
Current operating lease liabilities	Current portion of operating lease liabilities	$ 903	$ 10,992
Noncurrent operating lease liabilities	Operating lease liabilities, less current portion	5,129	33,727
Total operating lease liabilities		$ 6,032	$ 44,719
Finance lease liabilities (1):			
Current finance lease liabilities	Accounts payable and accrued expenses	$ —	$ 6,841
Noncurrent finance lease liabilities	Other liabilities	1,392	18,374
Total finance lease liabilities		$ 1,392	$ 25,215

(1) Amounts at December 31, 2022 exclude operating lease liabilities of $28 4 million and finance lease liabilities of $17 1 million that are classified as Liabilities subject to compromise in the Consolidated Balance Sheets

The following table presents information about lease costs and expenses and sublease income for the years ended December 31, 2022, 2021 and 2020 (in thousands):

	Statement of Operations Line Items	2022	2021	2020
Operating lease cost	Various (1)	$ 10,959	$ 13,892	$ 14,175
Finance lease cost:				
Amortization of right-of-use assets	Various (1)	$ 8,479	$ 9,244	$ 9,244
Interest on lease liabilities	Interest expense, net	$ 1,127	$ 1,480	$ 1,716
Other lease costs and income:				
Variable lease costs (2)	Various (1)	$ 11,707	$ 13,202	$ 10,305
Finance lease right-of-use asset impairment charges	Asset impairment charges	$ 3,063	$ —	$ —
Operating lease right-of-use asset impairment charges	Asset impairment charges	$ —	$ —	$ 6,392
Sublease income	Various (1)	$ (6,436)	$ (3,793)	$ (3,803)

(1) Amounts are included in the Consolidated Statements of Operations based on the function that the underlying leased asset supports The following table presents the components of such aggregate amounts for the years ended December 31, 2022, 2021 and 2020 (in thousands):

	2022	2021	2020
Cost of revenues	$ 6,189	$ 11,316	$ 11,610
Selling, general and administrative	$ 18,305	$ 21,013	$ 18,108
Research and development	$ 215	$ 216	$ 203

(2) Amounts represent variable lease costs incurred that were not included in the initial measurement of the lease liability such as common area maintenance and utilities costs associated with leased real estate and certain costs associated with our automobile leases

The following table provides the undiscounted amount of future cash flows included in our lease liabilities at December 31, 2022 for each of the five years subsequent to December 31, 2022 and thereafter, as well as a reconciliation of such undiscounted cash flows to our lease liabilities at December 31, 2022 (in thousands):

	Operating Leases	Finance Leases
2023	$ 11,518	$ 7,881
2024	6,599	8,038
2025	5,381	896
2026	5,337	896
2027	5,345	896
Thereafter	4,630	9,303
Total future lease payments	$ 38,810	$ 27,910
Less: amounts representing interest	4,391	9,440
Present value of future lease payments (lease liabilities, including amounts classified as Liabilities subject to compromise)	$ 34,419	$ 18,470
Less: amounts classified as Liabilities subject to compromise	28,387	17,078
Lease liabilities, excluding amounts classified as Liabilities subject to compromise	$ 6,032	$ 1,392

The following table provides the weighted average remaining lease term and weighted average discount rates for our leases as of December 31, 2022 and December 31, 2021:

	December 31, 2022	December 31, 2021
Weighted average remaining lease term (years), weighted based on lease liability balances:		
Operating leases	4.9 years	5.1 years
Finance leases	9.9 years	9.5 years
Weighted average discount rate (percentages), weighted based on the remaining balance of lease payments:		
Operating leases	6.1 %	5.9 %
Finance leases	7.5 %	7.6 %

The following table provides certain cash flow and supplemental noncash information related to our lease liabilities for the years ended December 31, 2022, 2021 and 2020 (in thousands):

	2022	2021	2020
Cash paid for amounts included in the measurement of lease liabilities:			
Operating cash payments for operating leases	$ 13,152	$ 14,478	$ 14,598
Operating cash payments for finance leases	$ 1,673	$ 2,256	$ 2,666
Financing cash payments for finance leases	$ 6,062	$ 5,448	$ 4,884
Lease liabilities arising from obtaining right-of-use assets:			
Operating leases (1)	$ 1,296	$ 5,807	$ —

(1) The amount in 2022 primarily relates to a new lease agreement The amount in 2021 primarily relates to an increase in lease liabilities and right-of-use assets related to a lease modification

NOTE 10. PROPERTY, PLANT AND EQUIPMENT

Property, plant and equipment, net consists of the following at December 31, 2022 and December 31, 2021 (in thousands):

	December 31, 2022	December 31, 2021
Land and buildings	$ 239,207	$ 234,219
Machinery and equipment	241,930	206,971
Leasehold improvements	54,388	55,020
Computer equipment and software	92,566	118,959
Furniture and fixtures	9,129	11,939
Assets under construction	142,560	120,483
Total property, plant and equipment, gross	$ 779,780	$ 747,591
Less: accumulated depreciation	(341,466)	(350,879)
Total property, plant and equipment, net	$ 438,314	$ 396,712

Depreciation expense was $54.3 million, $84.2 million and $91.3 million for the years ended December 31, 2022, 2021 and 2020, respectively. During the years ended December 31, 2022, 2021 and 2020, the Company recorded property, plant and equipment impairment charges totaling $9.0 million, $2.0 million and $1.2 million, respectively. These charges are included in the Asset impairment charges line item in our Consolidated Statements of Operations and primarily reflect the write-off of certain property, plant and equipment.

At December 31, 2022 and December 31, 2021, $205.2 million and $162.1 million of the Company's Property, plant and equipment, net, representing net book amounts, were located in India. At December 31, 2022 and December 31, 2021, there were no other material tangible long-lived assets located outside of the U.S., individually or in the aggregate.

NOTE 11. GOODWILL AND OTHER INTANGIBLES

Goodwill

Changes in the carrying amounts of our goodwill for the years ended December 31, 2022 and December 31, 2021 were as follows (in thousands):

	Branded Pharmaceuticals	Sterile Injectables	Generic Pharmaceuticals	International Pharmaceuticals	Total
Goodwill as of December 31, 2020	$ 828,818	$ 2,731,193	$ —	$ —	$ 3,560,011
Goodwill impairment charges	—	(363,000)	—	—	(363,000)
Goodwill as of December 31, 2021	$ 828,818	$ 2,368,193	$ —	$ —	$ 3,197,011
Goodwill impairment charges	—	(1,845,000)	—	—	(1,845,000)
Goodwill as of December 31, 2022	$ 828,818	$ 523,193	$ —	$ —	$ 1,352,011

The carrying amounts of goodwill at December 31, 2022 and December 31, 2021 are net of the following accumulated impairments (in thousands):

	Branded Pharmaceuticals	Sterile Injectables	Generic Pharmaceuticals	International Pharmaceuticals	Total
Accumulated impairment losses as of December 31, 2021	$ 855,810	$ 363,000	$ 3,142,657	$ 550,355	$ 4,911,822
Accumulated impairment losses as of December 31, 2022	$ 855,810	$ 2,208,000	$ 3,142,657	$ 513,211	$ 6,719,678

Other Intangible Assets

Changes in the amounts of other intangible assets for the year ended December 31, 2022 are set forth in the table below (in thousands).

Cost basis:	Balance as of December 31, 2021	Acquisitions	Impairments	Effect of Currency Translation	Balance as of December 31, 2022
Licenses (weighted average life of 14 years)	$ 442,107	$ —	$ —	$ —	$ 442,107
Tradenames	6,409	—	—	—	6,409
Developed technology (weighted average life of 12 years)	6,226,139	—	(288,701)	(17,417)	5,920,021
Total other intangibles (weighted average life of 12 years)	$ 6,674,655	$ —	$ (288,701)	$ (17,417)	$ 6,368,537

Accumulated amortization:	Balance as of December 31, 2021	Amortization	Impairments	Effect of Currency Translation	Balance as of December 31, 2022
Licenses	$ (419,932)	$ (4,576)	$ —	$ —	$ (424,508)
Tradenames	(6,409)	—	—	—	(6,409)
Developed technology	(3,885,491)	(332,735)	—	13,541	(4,204,685)
Total other intangibles	$ (4,311,832)	$ (337,311)	$ —	$ 13,541	$ (4,635,602)
Net other intangibles	$ 2,362,823				$ 1,732,935

Amortization expense for the years ended December 31, 2022, 2021 and 2020 totaled $337.3 million, $372.9 million and $427.5 million, respectively. Amortization expense is included in Cost of revenues in the Consolidated Statements of Operations. For intangible assets subject to amortization, estimated amortization expense for the five fiscal years subsequent to December 31, 2022 is as follows (in thousands):

2023	$ 255,869
2024	$ 245,751
2025	$ 232,668
2026	$ 209,532
2027	$ 134,364

Impairments

Goodwill and, if applicable, indefinite-lived intangible assets are tested for impairment annually, as of October 1, and when events or changes in circumstances indicate that the asset might be impaired.

As part of our goodwill and intangible asset impairment assessments, we estimate the fair values of our reporting units and our intangible assets using an income approach that utilizes a discounted cash flow model or, where appropriate, a market approach.

The discounted cash flow models reflect our estimates of future cash flows and other factors including estimates of: (i) future operating performance, including future sales, long-term growth rates, gross margins, operating expenses, discount rates and the probability of achieving the estimated cash flows, and (ii) future economic conditions. These assumptions are based on significant inputs and judgments not observable in the market, and thus represent Level 3 measurements within the fair value hierarchy. The discount rates used in the determination of fair value reflect our judgments regarding the risks and uncertainties inherent in the estimated future cash flows and may differ over time depending on the risk profile of the particular assets and other market factors. We believe the discount rates and other inputs and assumptions are consistent with those a market participant would use. Any impairment charges resulting from annual or interim goodwill and intangible asset impairment assessments are recorded to Asset impairment charges in our Consolidated Statements of Operations.

Annual Goodwill Impairment Tests

The Company performed its annual goodwill impairment tests as of October 1, 2022, 2021 and 2020. For the purposes of these annual tests, the Company had two reporting units with goodwill: Branded Pharmaceuticals and Sterile Injectables. The discount rates used for the Branded Pharmaceuticals reporting units in these annual tests were 15.0%, 14.5% and 15.0%, respectively, and the discount rates used for the Sterile Injectables reporting units in these annual tests were 19.5%, 11.0% and 10.0%, respectively.

As a result of our annual tests performed as of October 1, 2021, the Company determined that the carrying amount of the Sterile Injectables reporting unit exceeded its estimated fair value; therefore, the Company recorded a pre-tax non-cash goodwill impairment charge of $363.0 million during the fourth quarter of 2021. The Sterile Injectables impairment was primarily a result of changes in assumptions related to competition, including assumptions related to competing generic alternatives to VASOSTRICT®, which were subsequently introduced beginning with Eagle's at-risk launch in January 2022.

We did not record any other goodwill impairment charges as a result of our October 1, 2022, 2021 and 2020 annual impairment tests.

First-Quarter 2020 Interim Goodwill Impairment Test

As a result of certain business decisions that occurred during the first quarter of 2020, we tested the goodwill of our Paladin reporting unit for impairment as of March 31, 2020. The fair value of the reporting unit was estimated using an income approach that utilized a discounted cash flow model. The discount rate utilized in this test was 9.5%. This goodwill impairment test resulted in a pre-tax non-cash goodwill impairment charge of $32.8 million during the three months ended March 31, 2020, representing the remaining carrying amount. This impairment was primarily attributable to portfolio decisions and updated market expectations during the quarter.

Second-Quarter 2022 Interim Goodwill Impairment Tests

Beginning in May 2022, our share price and the aggregate estimated fair value of our debt experienced significant declines. We believe these declines, which persisted through the end of the second quarter of 2022, were predominantly attributable to continuing and increasing investor and analyst uncertainty with respect to: (i) ongoing opioid and other litigation matters for which we had been unable to reach a broad-based resolution of outstanding claims and (ii) speculation surrounding the possibility of a bankruptcy filing. Further, rising inflation and interest rates unfavorably affected the cost of borrowing, which is one of several inputs used in the determination of the discount rates used in our discounted cash flow models. For example, the U.S. Federal Reserve raised its benchmark interest rate by 50 basis points in May 2022 and by an additional 75 basis points in June 2022. Taken together, we determined that these factors represented triggering events that required the performance of interim goodwill impairments tests for both our Sterile Injectables and Branded Pharmaceuticals reporting units as of June 30, 2022.

When performing these goodwill impairment tests, we estimated the fair values of our reporting units taking into consideration management's continued commitment to Endo's strategic plans and the corresponding projected cash flows, as well as the fact that management's views on litigation risk had not materially changed since our annual goodwill impairment tests performed on October 1, 2021. However, when analyzing our aggregated estimated internal valuation of our reporting units as of June 30, 2022 compared to our market capitalization and the aggregate estimated fair value of our debt, we also considered the increased level of investor and analyst uncertainty described above, coupled with our belief that investors and analysts were unlikely to modify their projections or valuation models unless or until we could demonstrate significant progression on the resolution of outstanding litigation matters and/or demonstrate that the risks of potential future strategic alternatives, including the possibility of a future bankruptcy filing, were no longer applicable. After performing this analysis, we made certain adjustments to incorporate these factors into the valuations of our reporting units, primarily through adjustments to the discount rate resulting from an increase in the company-specific risk premium (CSRP), and determined that: (i) the estimated fair value of our Sterile Injectables reporting unit was less than its carrying amount, resulting in a pre-tax non-cash goodwill impairment charge of $1,748.0 million, and (ii) while the estimated fair value declined, there was no goodwill impairment for our Branded Pharmaceuticals reporting unit, for which the estimated fair value exceeded the carrying amount by more than 10%. The discount rates used in the June 30, 2022 goodwill tests were 13.5% and 18.5% for the Branded Pharmaceuticals and Sterile Injectables reporting units, respectively.

Third-Quarter 2022 Interim Goodwill Impairment Tests

As further described in Note 2. Bankruptcy Proceedings, during the third quarter of 2022, in connection with the Sale, we received the Stalking Horse Bid, subject to higher or otherwise better bids from other parties. The value of the bid, as well as our market capitalization and the aggregate estimated fair value of our debt, was considered when determining whether it was more likely than not that the carrying amounts of one or more of our reporting units exceeded their respective fair values. Further, rising inflation and interest rates unfavorably affected the cost of borrowing, which is one of several inputs used in the determination of the discount rates used in our discounted cash flow models. For example, the U.S. Federal Reserve raised its benchmark interest rate by 75 basis points in July 2022 and by an additional 75 basis points in September 2022. Taken together, we determined that these factors represented triggering events that required the performance of interim goodwill impairments tests for both our Sterile Injectables and Branded Pharmaceuticals reporting units as of September 30, 2022.

When performing these goodwill impairment tests, we estimated the fair values of our reporting units taking into consideration management's continued commitment to Endo's strategic plans and the corresponding projected cash flows. However, when analyzing our aggregated estimated internal valuation of our reporting units as of September 30, 2022 compared to our market capitalization and the aggregate estimated fair value of our debt, as well as the par value and fair value of the Stalking Horse Bid, we made adjustments to reflect certain risks and uncertainties, including those related to the Chapter 11 Cases and the Sale, into the valuations of our reporting units, primarily through adjustments to the discount rate resulting from an increase in the CSRP, and determined that: (i) the estimated fair value of our Sterile Injectables reporting unit was less than its carrying amount, resulting in a pre-tax non-cash goodwill impairment charge of $97.0 million, and (ii) the estimated fair value of our Branded Pharmaceuticals reporting unit exceeded the carrying amount by more than 10%. The discount rates used in the September 30, 2022 goodwill tests were 15.0% and 19.5% for the Branded Pharmaceuticals and Sterile Injectables reporting units, respectively.

Fourth-Quarter 2022 Interim Goodwill Impairment Test

Beginning in late fourth-quarter 2022 and concluding in February 2023, the Company completed its annual enterprise-wide long-term strategic planning process, which resulted in updates to its projected future cash flows. Among other items, these updates primarily reflected the anticipated impacts on the Company's projected future cash flows resulting from: (i) the discontinuation of QWO®; (ii) the disruption to XIAFLEX® revenues that occurred in the second half of 2022; (iii) routine updates to our assumptions regarding anticipated competitive events for currently marketed products, as well as probabilities of success, launch timing and the anticipated competitive landscape surrounding new product launches, including with respect to TLC599 and certain product candidates in our Sterile Injectables reporting unit pipeline; (iv) expected changes in the Company's future manufacturing expense profile, including delays related to construction, FDA inspections and product transfers to our Sterile Injectables facility in Indore, India; and (v) changes in the Company's future operating expense profile. Due to the extent of the changes to the projected future cash flows, coupled with the fact that we had recorded impairments for our Sterile Injectables reporting unit during the second and third quarters of 2022, we concluded that it was more likely than not that the carrying amount of our Sterile Injectables reporting unit may exceed its fair value. As a result, an interim impairment test was performed as of December 31, 2022. The updates to the projected future cash flows did not result in an interim goodwill impairment test for our Branded Pharmaceuticals reporting unit due to the significant headroom in this reporting unit.

When performing the goodwill impairment test, we estimated the fair value of our Sterile Injectables reporting unit taking into consideration management's updated forecasts of projected cash flows, as further discussed above. The updated forecast of projected future cash flows was reduced in comparison to the prior 2022 tests. However, in reducing the cash flows, we believe the level of risk and uncertainty of the cash flows also decreased resulting in a corresponding decrease in the CSRP and, in turn, the discount rate used in the determination of fair value of our Sterile Injectables reporting unit. The discount rate used in the December 31, 2022 goodwill impairment test was 14.5%. We believe this discount rate and the other inputs and assumptions used to estimate fair value were consistent with those that a market participant would have used in light of the degree of risk associated with the updated estimated future cash flows. Consistent with the goodwill impairment tests performed earlier in 2022, we compared our aggregated estimated internal valuation of our reporting units as of December 31, 2022 to our market capitalization and the aggregate estimated fair value of our debt, as well as the par value and fair value of the Stalking Horse Bid. As a result of the December 31, 2022 test, we determined that there was no impairment of goodwill.

Other Intangible Asset Impairments

With respect to other intangible assets, we recorded asset impairment charges of $288.7 million, $7.8 million and $79.9 million during the years ended December 31, 2022, 2021 and 2020, respectively. These pre-tax non-cash asset impairment charges related primarily to certain developed technology intangible assets that were tested for impairment following changes in market conditions and certain other factors impacting recoverability. The amount recorded in 2022 included charges related to the 2022 Restructuring Initiative, as further discussed in Note 5. Restructuring.

NOTE 12. LICENSE, COLLABORATION AND ASSET ACQUISITION AGREEMENTS

We have entered into certain license, collaboration and asset acquisition agreements with third parties. Generally, these agreements require us to share in the costs of developing, manufacturing, commercializing and/or selling product candidates and/or products with third parties, who in turn grant us marketing rights for such product candidates and/or products. Under these agreements we are generally required to: (i) make upfront payments and/or other payments upon successful completion of regulatory, sales and/or other milestones and/or (ii) pay royalties on sales and/or other costs arising from these agreements. We have also, from time to time, entered into agreements to directly acquire certain assets from third parties.

BioSpecifics

On October 19, 2020, the Company entered into an Agreement and Plan of Merger (the Merger Agreement) with Beta Acquisition Corp., a Delaware corporation and wholly-owned indirect subsidiary of the Company (Merger Sub) and BioSpecifics. Pursuant to the Merger Agreement, and on the terms and subject to the conditions thereof, Merger Sub commenced a tender offer (the Offer) on November 2, 2020 to acquire all of BioSpecifics' issued and outstanding shares of common stock (BioSpecifics Shares) at a purchase price of $88.50 per BioSpecifics Share, net to the holder thereof in cash, subject to reduction for any applicable withholding taxes and without interest.

Through the expiration of the Offer on December 1, 2020, approximately 6,159,975 BioSpecifics Shares were validly tendered and not validly withdrawn in accordance with the terms of the Offer. With all conditions to the Offer satisfied, on December 2, 2020, Merger Sub accepted for purchase all of the BioSpecifics Shares that were validly tendered and not validly withdrawn in accordance with the terms of the Offer.

Following consummation of the Offer, on December 2, 2020, Merger Sub merged with and into BioSpecifics (the Merger) in accordance with Section 251(h) of the Delaware General Corporation Law without a vote on the adoption of the Merger Agreement by BioSpecifics' stockholders, with BioSpecifics continuing as the surviving corporation in the Merger and thereby becoming a wholly-owned, indirect subsidiary of the Company.

As a result of the Merger, the BioSpecifics Shares ceased to be traded on the Nasdaq, effective as of market open on December 2, 2020.

The operating results of BioSpecifics are included in the accompanying Consolidated Statements of Operations from December 2, 2020 and the assets and liabilities of BioSpecifics are included in the Consolidated Balance Sheets as of December 31, 2022 and 2021.

Prior to the Merger, BioSpecifics was a biopharmaceutical company involved in the development of injectable CCH that generated revenue primarily from a license agreement with us. We had a strategic relationship with BioSpecifics since 2004 pursuant to which BioSpecifics was, among other things, entitled to a royalty stream from us related to our collagenase-based therapies, including XIAFLEX®. Specifically, we were required to, among other things, pay BioSpecifics, on a country-by-country and product-by-product basis, a specified percentage, within a range of 5% to 15% of net sales, of certain specified products. This royalty applied to net sales by us and/or any of our sublicensees. In addition, we were required to pay BioSpecifics an amount equal to a specified mark-up on certain cost of goods related to supply of XIAFLEX® (which mark-up was capped at a specified percentage within the range of 5% to 15% of the cost of goods of XIAFLEX®). Our December 2020 acquisition of BioSpecifics eliminated this third-party relationship, which had the effect of reducing royalty payments recognized in Cost of revenues. The BioSpecifics acquisition also eliminated certain milestones and royalties we may otherwise have been required to pay for potential future indications of products or product candidates containing CCH, including those associated with our plantar fibromatosis development program.

The acquired set of BioSpecifics assets and activities did not meet the definition of a business based on our assessment that the acquired set of activities lacks substantive processes that significantly contribute to the conversion of inputs into outputs. As a result, we accounted for the transaction as an asset acquisition. The consideration transferred in the asset acquisition was measured at cost, including transaction costs, assets transferred by the Company and royalty obligations discharged by the seller. The following table represents the costs accumulated to acquire BioSpecifics (in thousands):

	December 2, 2020
Base purchase price (1)	$ 650,029
Vested employee options and benefits (2)	10,280
Transaction costs	10,268
Less: royalty obligations discharged (3)	(14,909)
Total acquisition consideration	$ 655,668

(1) Represents cash consideration paid for 6,159,975 shares tendered and 1,184,980 remaining shares not tendered, but automatically cancelled and funded in an escrow account
(2) In accordance with BioSpecifics' stock plan and employment arrangements, certain unvested options and employee bonus compensation immediately vested and accelerated, with no future service requirement, upon change in control We have accounted for the accelerated vestings as a component of consideration transferred
(3) Represents the total reduction to the base purchase price for the pre-acquisition accrued and unpaid royalty liability discharged on the date of closing

The following table summarizes the allocation of consideration transferred on a relative fair value basis to identifiable tangible and intangible assets and other information about the assets and liabilities acquired at the BioSpecifics acquisition date (in thousands):

	December 2, 2020
Cash and cash equivalents	$ 21,073
Investments (1)	89,050
Intangible assets—developed technology	673,796
Intangible assets—in-process research and development	28,602
Other acquired assets	3,089
Deferred tax liability	(156,441)
Other assumed liabilities	(3,501)
Net identifiable assets acquired	$ 655,668

(1) Investments acquired primarily consisted of debt securities acquired from BioSpecifics on December 2, 2020 Investments acquired were fully liquidated prior to December 31, 2020 No material gains or losses were recognized upon liquidation

The in-process research and development assets noted in the table above were expensed on the acquisition date and are included in Acquired in-process research and development in the Consolidated Statements of Operations. The Company concluded that the consideration allocable to developed technology acquired represented incremental costs associated with the Company's existing XIAFLEX® and QWO® intangible assets (the Existing Intangible Assets). The Existing Intangible Assets were acquired by the Company as part of its acquisition of Auxilium Pharmaceuticals, Inc. (Auxilium), accounted for as a business combination at fair value during 2015. Auxilium had a pre-existing development and license agreement with BioSpecifics. The following table summarizes changes to the gross carrying amount, accumulated amortization and net book amount of the Existing Intangible Assets and the new intangible assets resulting from the BioSpecifics acquisition (in thousands):

	Gross Carrying Amount	Accumulated Amortization	Net Book Amount
Asset balances immediately prior to BioSpecifics acquisition	$ 1,580,600	$ (725,123)	$ 855,477
Additional costs incurred in connection with BioSpecifics acquisition	673,796	—	673,796
Asset balances immediately following BioSpecifics acquisition	$ 2,254,396	$ (725,123)	$ 1,529,273

Prior to the BioSpecifics acquisition, the Company had been amortizing the Existing Intangible Assets over their respective useful lives, which were the periods over which the assets were expected to contribute directly or indirectly to the future cash flows of the Company. The BioSpecifics acquisition significantly impacted the timing and amount of estimated future cash flows from sales of XIAFLEX® and QWO® and, therefore, the Company considered the acquisition to be a triggering event to remeasure the expected useful lives of the XIAFLEX® and QWO® intangible assets. Immediately following the BioSpecifics acquisition, the Company determined that the weighted average useful life for the XIAFLEX® and QWO® intangible assets was approximately 13.6 years from the closing date of the BioSpecifics acquisition and, accordingly, the Company began to amortize the corresponding intangible assets prospectively on a straight-line basis over their then-anticipated useful lives, which approximated the periods of economic benefits expected to be realized from future cash flows from sales of XIAFLEX® and QWO®. The Company's accounting for these intangible assets has since been affected by certain subsequent developments, including the Company's plans announced in December 2022 that it would be ceasing the production and sale of QWO® in light of market concerns about the extent and variability of bruising following initial treatment as well as the potential for prolonged skin discoloration. Refer to Note 5. Restructuring for additional information.

Nevakar Agreements

In May 2022, we announced that our EVL subsidiary had entered into an agreement to acquire six development-stage RTU injectable product candidates from Nevakar Injectables, Inc., a subsidiary of Nevakar, Inc., for an upfront cash payment of $35.0 million (the 2022 Nevakar Agreement). The acquisition closed during the second quarter of 2022. The acquired set of assets and activities did not meet the definition of a business. As a result, we accounted for the transaction as an asset acquisition. Upon closing, the upfront payment was recorded as Acquired in-process research and development in the Consolidated Statements of Operations.

The product candidates, which relate to our Sterile Injectables segment, are in various stages of development. The first commercial launch is expected in 2025; however, there can be no assurance this will occur within this timeframe or at all. With this acquisition, the Company will control all remaining development, regulatory, manufacturing and commercialization activities for the acquired product candidates.

In August 2022, within the ongoing bankruptcy proceedings, EVL filed an adversary proceeding (the Nevakar Litigation) against Nevakar, Inc. and Nevakar Injectables Inc. (collectively, Nevakar) to enforce: (i) a 2018 development, license and commercialization agreement (the 2018 Nevakar Agreement) and (ii) the 2022 Nevakar Agreement. In September 2022, Nevakar filed counterclaims against EVL. In December 2022, EVL and Nevakar reached a settlement with respect to the Nevakar Litigation (the Nevakar Settlement) subject to Bankruptcy Court approval. The Nevakar Settlement provided for the amendment of the 2018 Nevakar Agreement to revoke EVL's license of two products covered by the 2018 Nevakar Agreement, modify EVL's license to the remaining three products covered by the 2018 Nevakar Agreement to reduce the royalty owed to Nevakar, terminate any obligations of EVL to make payments to Nevakar upon achievement of contingent milestones and eliminate Nevakar's ability to terminate the remaining licenses for EVL's breach or material breach. The Nevakar Settlement also provided that EVL and Nevakar would agree to a mutual release of certain claims under both the 2018 Nevakar Agreement and the 2022 Nevakar Agreement. The Nevakar Settlement was approved by the Bankruptcy Court in January 2023. The Nevakar Settlement had no effect on our Consolidated Financial Statements in 2022; we are currently evaluating how the Nevakar Settlement will be accounted for in 2023.

TLC Agreement

In June 2022, we announced that our EVL subsidiary had entered into an agreement with TLC to commercialize TLC599 (the TLC Agreement). We are accounting for the agreement as an asset acquisition. TLC599 is an injectable compound in Phase 3 development for the treatment of osteoarthritis knee pain.

Under the terms of the TLC Agreement, TLC is primarily responsible for the development of the product and we are primarily responsible for obtaining regulatory approval and for commercialization of the product in the U.S. Upon receipt of regulatory approval, if obtained, we will have exclusive rights to manufacture, market, sell and distribute the product in the U.S.

During the second quarter of 2022, we made an upfront payment of $30.0 million to TLC and recorded a corresponding charge to Acquired in-process research and development in the Consolidated Statements of Operations. TLC is also eligible to receive: (i) payments of up to an additional $110.0 million based on the achievement of certain development, regulatory and manufacturing milestones related to the initial indication for the treatment of osteoarthritis knee pain; (ii) payments of up to an additional $30.0 million based on the achievement of certain development and regulatory milestones related to certain potential future indications; (iii) payments of up to an additional $500.0 million based on the achievement of certain commercial milestones; and (iv) tiered royalties based on net sales of TLC599 in the U.S. Unless terminated earlier or extended, the term of the TLC Agreement generally extends until the 20-year anniversary of the first commercial sale of TLC599.

Pursuant to the terms of the TLC Agreement, we have deposited approximately $85.0 million of cash into a bank account which may be used to fund certain future obligations under the TLC Agreement or returned to us upon satisfaction of certain conditions. As further described in Note 7. Fair Value Measurements, this amount is considered restricted cash as of December 31, 2022 and is included in our Consolidated Balance Sheets at December 31, 2022 as Other assets.

In September 2022, we were informed by TLC of the top-line results from TLC's Phase 3 clinical study to evaluate the efficacy and safety of TLC599 in patients with pain from osteoarthritis of the knee. While study participants treated with TLC599 showed improvement on the primary endpoint (change from baseline to week 12 on the WOMAC pain scale) consistent with the level of improvement reported in the previously conducted TLC599 Phase 2 clinical study, the difference compared to those receiving placebo was not statistically significant. Based on these data, we are evaluating options for TLC599 with TLC.

NOTE 13. CONTRACT ASSETS AND LIABILITIES

Our revenue consists almost entirely of sales of our products to customers, whereby we ship products to a customer pursuant to a purchase order. Revenue contracts such as these do not generally give rise to contract assets or contract liabilities because: (i) the underlying contracts generally have only a single performance obligation and (ii) we do not generally receive consideration until the performance obligation is fully satisfied. At December 31, 2022, the unfulfilled performance obligations for these types of contracts relate to ordered but undelivered products. We generally expect to fulfill the performance obligations and recognize revenue within one week of entering into the underlying contract. Based on the short-term initial contract duration, additional disclosure about the remaining performance obligations is not required.

Certain of our other income-generating contracts, including license and collaboration agreements, may result in contract assets and/or contract liabilities. For example, we may recognize contract liabilities upon receipt of certain upfront and milestone payments from customers when there are remaining performance obligations.

The following table shows the opening and closing balances of contract assets and contract liabilities from contracts with customers (dollars in thousands):

	December 31, 2022	December 31, 2021	$ Change	% Change
Contract assets (1)	$ 8,193	$ 13,005	$ (4,812)	(37)%
Contract liabilities (2)	$ 4,099	$ 4,663	$ (564)	(12)%

(1) At December 31, 2022 and December 31, 2021, approximately $1 5 million and $2 8 million, respectively, of these contract asset amounts are classified as current and are included in Prepaid expenses and other current assets in the Company's Consolidated Balance Sheets The remaining amounts are classified as noncurrent and are included in Other assets The net decrease in contract assets during the year ended December 31, 2022 primarily relates to: (i) reclassifications of certain amounts to receivables as a result of rights to consideration becoming unconditional and (ii) net changes in estimates with respect to amounts of consideration expected to be received from sales of certain intellectual property rights

(2) At December 31, 2022 and December 31, 2021, approximately $0 6 million and $0 6 million, respectively, of these contract liability amounts are classified as current and are included in Accounts payable and accrued expenses in the Company's Consolidated Balance Sheets The remaining amounts are classified as noncurrent and are included in Other liabilities During the year ended December 31, 2022, approximately $0 6 million of revenue was recognized that was included in the contract liability balance at December 31, 2021

During the year ended December 31, 2022, we recognized revenue of $11.9 million relating to performance obligations satisfied, or partially satisfied, in prior periods. Such revenue generally relates to changes in estimates with respect to our variable consideration.

NOTE 14. ACCOUNTS PAYABLE AND ACCRUED EXPENSES

Accounts payable and accrued expenses included the following at December 31, 2022 and December 31, 2021 (in thousands):

	December 31, 2022	December 31, 2021
Trade accounts payable	$ 109,033	$ 123,129
Returns and allowances	160,619	183,116
Rebates	167,516	150,039
Chargebacks	920	2,617
Other sales deductions	6,197	2,500
Accrued interest	68	106,735
Accrued payroll and related benefits	95,666	90,029
Accrued royalties and other distribution partner payables	24,072	58,422
Acquisition-related contingent consideration—current	—	5,748
Other (1)	123,092	114,563
Total	$ 687,183	$ 836,898

(1) Amounts include a wide variety of accrued expenses, the most significant of which relate to accrued legal and other professional fees

The amounts in the table above do not include amounts classified as Liabilities subject to compromise in our Consolidated Balance Sheets. Refer to Note 2. Bankruptcy Proceedings for additional information about Liabilities subject to compromise.

NOTE 15. DEBT

The following table presents information about the Company's total indebtedness at December 31, 2022 and December 31, 2021 (dollars in thousands):

	December 31, 2022			December 31, 2021		
	Effective Interest Rate (1)	Principal Amount (2)	Carrying Amount (2)	Effective Interest Rate	Principal Amount	Carrying Amount
7.25% Senior Notes due 2022		$ —	$ —	7.25 %	$ 8,294	$ 8,294
5.75% Senior Notes due 2022		—	—	5.75 %	172,048	172,048
5.375% Senior Notes due 2023	5.38 %	6,127	6,127	5.62 %	6,127	6,111
6.00% Senior Notes due 2023	6.00 %	56,436	56,436	6.28 %	56,436	56,203
5.875% Senior Secured Notes due 2024	6.88 %	300,000	286,375	6.14 %	300,000	297,928
6.00% Senior Notes due 2025	6.00 %	21,578	21,578	6.27 %	21,578	21,413
7.50% Senior Secured Notes due 2027	8.50 %	2,015,479	1,894,774	7.70 %	2,015,479	1,997,777
9.50% Senior Secured Second Lien Notes due 2027	9.50 %	940,590	940,590	9.68 %	940,590	933,330
6.00% Senior Notes due 2028	6.00 %	1,260,416	1,260,416	6.11 %	1,260,416	1,252,667
6.125% Senior Secured Notes due 2029	7.13 %	1,295,000	1,230,799	6.34 %	1,295,000	1,278,718
Term Loan Facility	13.50 %	1,975,000	1,871,894	6.12 %	1,985,000	1,947,633
Revolving Credit Facility	11.00 %	277,200	265,728	2.63 %	277,200	277,200
Total (3)		$ 8,147,826	$ 7,834,717		$ 8,338,168	$ 8,249,322

(1) As noted below, beginning on the Petition Date, we ceased recognition of interest expense related to all of our debt instruments and began to incur "adequate protection payments" (further discussed below) related to our First Lien Debt Instruments (representing all of our debt instruments except for our senior unsecured notes and the 9 50% Senior Secured Second Lien Notes due 2027) The December 31, 2022 "effective interest rates" included in the table above represent the rates in effect on such date used to calculate: (i) future adequate protection payments related to our First Lien Debt Instruments and (ii) future contractual interest related to our other debt instruments, notwithstanding the fact that such interest is not currently being recognized These rates are expressed as a percentage of the contractual principal amounts outstanding as of such date and, with respect to our First Lien Debt Instruments, without consideration of any reductions related to adequate protection payments made through such date

(2) The December 31, 2022 principal amounts represent the amount of unpaid contractual principal owed on the respective instruments During the third quarter of 2022, in accordance with ASC 852, we adjusted the carrying amounts of all unsecured and potentially undersecured debt instruments to equal the expected amount of the allowed claim by expensing (within Reorganization items, net in the Consolidated Statements of Operations) $89 2 million of previously-deferred and unamortized costs associated with these instruments The December 31, 2022 carrying amounts of our First Lien Debt Instruments also reflect reductions for certain adequate protection payments made since the Petition Date, as further discussed herein

(3) As of December 31, 2022, the entire carrying amount our debt, as well as any related remaining accrued and unpaid interest that existed as of the Petition Date, is included in the Liabilities subject to compromise line in the Consolidated Balance Sheets As of December 31, 2021, $200 3 million of the carrying amount of our debt is classified as a current liability and is included in the Current portion of long-term debt line in the Consolidated Balance Sheets The remaining carrying amount of our debt as of December 31, 2021 is included in the Long-term debt, less current portion, net line in the Consolidated Balance Sheets

General Information

The Company and its subsidiaries, with certain customary exceptions, guarantee or serve as issuers or borrowers of the debt instruments representing substantially all of the Company's indebtedness at December 31, 2022. The obligations under: (i) the 5.875% Senior Secured Notes due 2024; (ii) the 7.50% Senior Secured Notes due 2027; (iii) the 6.125% Senior Secured Notes due 2029; and (iv) the Credit Agreement and related loan documents are secured on a *pari passu* basis by a first priority lien (subject to certain permitted liens) on the collateral securing such instruments, which collateral represents substantially all of the assets of the issuers or borrowers and guarantors party thereto (subject to customary exceptions). The obligations under the 9.50% Senior Secured Second Lien Notes due 2027 are secured by a second priority lien (subject to certain permitted liens) on, and on a junior basis with respect to, the collateral securing the obligations under the Credit Agreement, the 5.875% Senior Secured Notes due 2024, the 7.50% Senior Secured Notes due 2027 and the 6.125% Senior Secured Notes due 2029 and the related guarantees. Our senior unsecured notes are unsecured and effectively subordinated in right of priority to the obligations under the Credit Agreement, the 5.875% Senior Secured Notes due 2024, the 7.50% Senior Secured Notes due 2027, the 9.50% Senior Secured Second Lien Notes due 2027 and the 6.125% Senior Secured Notes due 2029, in each case to the extent of the value of the collateral securing such instruments.

The aggregate estimated fair value of the Company's long-term debt, which was estimated using inputs based on quoted market prices for the same or similar debt issuances, was $4.9 billion and $8.0 billion at December 31, 2022 and December 31, 2021, respectively. Based on this valuation methodology, we determined these debt instruments represent Level 2 measurements within the fair value hierarchy.

Credit Facilities

The Company and certain of its subsidiaries are party to the Credit Agreement, which immediately following the March 2021 Refinancing Transactions provided for: (i) a $1,000.0 million senior secured revolving credit facility (the Revolving Credit Facility) and (ii) a $2,000.0 million senior secured term loan facility (the Term Loan Facility and, together with the Revolving Credit Facility, the Credit Facilities).

Current amounts outstanding as of December 31, 2022 under the Credit Facilities are set forth in the table above.

Principal payments on the Term Loan Facility equal to 0.25% of the initial $2,000.0 million principal amount are generally payable quarterly, beginning on June 30, 2021 and extending until the Term Loan Facility's maturity date in March 2028, at which time the remaining principal amount outstanding is payable. Based on the Company's borrowings under the Revolving Credit Facility outstanding at December 31, 2022, $74.6 million generally matures in 2024, with the remainder generally maturing in 2026.

Borrowings under the Revolving Credit Facility bear interest, at the borrower's election, at a rate per annum equal to: (i) an applicable margin between 1.50% and 3.00% depending on the Company's Total Net Leverage Ratio plus the Adjusted LIBO Rate (as defined in the Credit Agreement) or (ii) an applicable margin between 0.50% and 2.00% depending on the Company's Total Net Leverage Ratio plus the Alternate Base Rate (as defined in the Credit Agreement). In addition, borrowings under our Term Loan Facility bear interest, at the borrower's election, at a rate per annum equal to: (i) 5.00% plus the Adjusted LIBO Rate, subject to a London Interbank Offered Rate (LIBOR) floor of 0.75%, or (ii) 4.00% plus the Alternate Base Rate, subject to an Alternate Base Rate floor of 1.75%. Interest on these instruments is generally payable at the end of each interest period but at least every three months.

The foregoing summary, which does not purport to be complete, is based on the terms of the Credit Agreement. Refer to the "Covenants, Events of Default and Bankruptcy-Related Matters" section below for a discussion of the effects of the ongoing bankruptcy proceedings and the related event of default on the Credit Facilities.

Senior Notes and Senior Secured Notes

The various senior notes and senior secured notes outstanding as of December 31, 2022 generally mature between 2023 and 2029. Interest on these notes is generally payable semiannually in arrears. The indentures governing these notes generally allow for redemption prior to maturity, in whole or in part, subject to certain restrictions and limitations described therein. The foregoing summary, which does not purport to be complete, is based on the terms of the indentures governing our various senior notes and senior secured notes. Refer to the "Covenants, Events of Default and Bankruptcy-Related Matters" section below for a discussion of the effects of the ongoing bankruptcy proceedings and the related event of default on our various senior notes and senior secured notes.

Covenants, Events of Default and Bankruptcy-Related Matters

The agreements relating to our outstanding indebtedness contain certain covenants and events of default.

Beginning during the second quarter of 2022, we elected to not make the following interest payments on or prior to their scheduled due dates: (i) approximately $38 million that was due on June 30, 2022 with respect to our outstanding 6.00% Senior Notes due 2028; (ii) approximately $2 million that was due on July 15, 2022 with respect to our outstanding 5.375% Senior Notes due 2023 and 6.00% Senior Notes due 2023; (iii) approximately $45 million that was due on July 31, 2022 with respect to our outstanding 9.50% Senior Secured Second Lien Notes due 2027; and (iv) approximately $1 million that was due on August 1, 2022 with respect to our outstanding 6.00% Senior Notes due 2025. Under each of the indentures governing these notes, we had a 30-day grace period from the respective due dates to make these interest payments before such non-payments constituted events of default with respect to such notes. We chose to enter these grace periods while continuing discussions with certain creditors in connection with our evaluation of strategic alternatives. Our decision to enter these grace periods was not driven by liquidity constraints. We made the interest payment of approximately $38 million that became due on June 30, 2022 with respect to our outstanding 6.00% Senior Notes due 2028 on July 28, 2022, which was prior to the end of the applicable grace period. We also made the interest payments totaling approximately $2 million that became due on July 15, 2022 with respect to our outstanding 5.375% Senior Notes due 2023 and 6.00% Senior Notes due 2023 on August 11, 2022, which was prior to the end of the applicable grace periods.

On the Petition Date, the Debtors filed voluntary petitions for relief under the Bankruptcy Code, which constituted an event of default that accelerated our obligations under substantially all of our then-outstanding debt instruments. However, section 362 of the Bankruptcy Code stays creditors from taking any action to enforce the related financial obligations and creditors' rights of enforcement in respect of the debt instruments are subject to the applicable provisions of the Bankruptcy Code.

As a result of the Chapter 11 Cases, since the Petition Date, we have not made, and we are not currently making, any scheduled principal or interest payments on the Credit Facilities or our various senior notes and senior secured notes. We are however making certain adequate protection payments as further discussed below. Additionally, as a result of the Chapter 11 Cases, all remaining commitments under the Revolving Credit Facility have been terminated.

The transactions contemplated by the RSA are subject to approval by the Bankruptcy Court, among other conditions. Accordingly, no assurance can be given that the transactions described therein will be consummated. Because the Company has not yet obtained approval by the Bankruptcy Court regarding such transactions, there remains uncertainty with respect to the ability of our creditors, including our secured and unsecured debt holders, to recover the full amount of their claims against us. As a result, all secured and unsecured debt instruments have been classified as Liabilities subject to compromise in our Consolidated Balance Sheets as of December 31, 2022 and we ceased the recognition of interest expense related to these instruments as of the Petition Date. During 2022, we did not recognize approximately $231 million of contractual interest expense that would have been recognized if not for the Chapter 11 Cases.

As part of the RSA that is further discussed in Note 2. Bankruptcy Proceedings, the Company and the Ad Hoc First Lien Group agreed on the terms of a proposed order authorizing the Company's use of cash collateral (as modified and entered by the Bankruptcy Court on a final (amended) basis in October 2022, the Cash Collateral Order) in connection with the Chapter 11 Cases on certain terms and conditions set forth therein.

Pursuant to the Cash Collateral Order, we are obligated to make certain adequate protection payments during our bankruptcy proceedings on each of our First Lien Debt Instruments. These adequate protection payments include the payment of amounts equal to any accrued and unpaid interest that existed as of the Petition Date by no later than eight business days after entry of the interim Cash Collateral Order, as well as the following payments, to be paid on the last business day of each calendar month, calculated based upon a rate of:

- with respect to the Revolving Credit Facility and the Term Loan Facility, 200 basis points plus: (i) if denominated in dollars, ABR plus the Applicable Rate (each as defined in the Credit Agreement), or (ii) if denominated in Canadian dollars, the Canadian Prime Rate plus the Applicable Rate (each as defined in the Credit Agreement); and
- with respect to the applicable senior secured notes, 100 basis points plus the applicable rate of interest set forth on the face of the applicable note.

The rates in the foregoing bullet points, which are used to calculate any applicable adequate protection payments, are expressed as a percentage of the contractual principal amounts outstanding without consideration of any reductions related to adequate protection payments. On a cumulative basis through December 31, 2022, we made the following adequate protection payments pursuant to the Cash Collateral Order:

- $11.5 million with respect to the Revolving Credit Facility;
- $103.1 million with respect to the Term Loan Facility; and
- $198.5 million with respect to the applicable senior secured notes.

As required by ASC 852, these adequate protection payments are recorded as a reduction of the carrying amount of the respective First Lien Debt Instruments, which are classified as Liabilities subject to compromise. This accounting treatment is due to the aforementioned uncertainties with respect to the ultimate outcome of the bankruptcy proceedings, including the proposed Sale transaction, which in turn creates uncertainties surrounding the first lien debt holders' ability to recover in full the amount of outstanding principal associated with those instruments. Some or all of the adequate protection payments may later be recharacterized as interest expense depending upon certain developments in the Chapter 11 Cases.

In addition to the terms described above, the Cash Collateral Order, among other things, establishes a budget for the Debtors' use of cash collateral, establishes certain informational rights for the Debtors' secured creditors and provides for the waiver of certain Bankruptcy Code provisions. The foregoing description of the Cash Collateral Order does not purport to be complete and is qualified in its entirety by reference to the Cash Collateral Order entered by the Bankruptcy Court in the Chapter 11 Cases.

Debt Financing Transactions

Set forth below are certain disclosures relating to debt financing transactions that occurred during the years ended December 31, 2022, 2021 and 2020.

June 2020 Refinancing

In June 2020, the Company executed certain transactions (the June 2020 Refinancing Transactions) that included, among other things, the exchanges by certain of the Company's wholly-owned subsidiaries of certain series of senior notes for certain newly issued senior secured notes and senior notes and $47.2 million in cash paid by the Company. The June 2020 Refinancing Transactions
were accounted for as debt modifications. Following the June 2020 Refinancing Transactions, previously deferred and unamortized amounts associated with the old notes exchanged began to be amortized over the respective terms of the new notes; this continued until the initiation of our bankruptcy proceedings during the third quarter of 2022, at which time the remaining unamortized costs were expensed as Reorganization items, net in the Consolidated Statements of Operations. In connection with the June 2020 Refinancing Transactions, we incurred fees to third parties of approximately $31.1 million, substantially all of which were charged to expense during the second quarter of 2020 and were included in Selling, general and administrative expenses in the Consolidated Statements of Operations.

August 2020 Tender Offer

In August 2020, the Company repurchased and retired approximately $10 million in aggregate principal of 5.75% Senior Notes due 2022 pursuant to a tender offer.

March 2021 Refinancing

In March 2021, the Company executed certain transactions (the March 2021 Refinancing Transactions) that included:

- refinancing in full its previously-existing term loans, which had approximately $3,295.5 million of principal outstanding immediately before refinancing (the Existing Term Loans), with the proceeds from: (i) a new $2,000.0 million term loan (the Term Loan Facility) and (ii) $1,295.0 million of newly issued 6.125% Senior Secured Notes due 2029 (collectively, the Term Loan Refinancing);
- extending the maturity of approximately $675.3 million of existing revolving commitments under the Revolving Credit Facility to March 2026; and
- making certain other modifications to the credit agreement that was in effect immediately prior to the March 2021 Refinancing Transactions (the Prior Credit Agreement).

The changes to the Credit Facilities and the Prior Credit Agreement were effected pursuant to an amendment and restatement agreement entered into by the Company in March 2021 (the Restatement Agreement), which amended and restated the Prior Credit Agreement (as amended and restated by the Restatement Agreement, the Credit Agreement), among Endo International plc, certain of its subsidiaries, the lenders party thereto and JPMorgan Chase Bank, N.A., as administrative agent, issuing bank and swingline lender.

The $2,000.0 million portion of the Term Loan Refinancing associated with the new term loan was accounted for as a debt modification, while the $1,295.0 million portion associated with the new notes issued was accounted for as an extinguishment. During the first quarter of 2021, in connection with the Term Loan Refinancing, $7.8 million of deferred and unamortized costs associated with the Existing Term Loans, representing the portion associated with the extinguishment, was charged to expense and is included in the Loss on extinguishment of debt line item in the Consolidated Statements of Operations. The Company also incurred an additional $56.7 million of new costs and fees, of which: (i) $29.2 million and $17.6 million were initially deferred to be amortized as interest expense over the terms of the Term Loan Facility and the newly issued 6.125% Senior Secured Notes due 2029, respectively; (ii) $6.0 million was considered debt extinguishment costs and was charged to expense in the first quarter of 2021 and is included in the Loss on extinguishment of debt line item in the Consolidated Statements of Operations; and (iii) $3.9 million was considered debt modification costs and was charged to expense in the first quarter of 2021 and is included in the Selling, general and administrative expense line item in the Consolidated Statements of Operations. The deferred amounts were being amortized as interest expense until the initiation of our bankruptcy proceedings during the third quarter of 2022, at which time the remaining unamortized costs were expensed as Reorganization items, net in the Consolidated Statements of Operations.

During the first quarter of 2021, the Company also incurred $2.1 million of new costs and fees associated with the extension of the Revolving Credit Facility, which have been deferred and are being amortized as interest expense over the new term of the Revolving Credit Facility.

October 2021 Revolving Credit Facility Repayment and January 2022 Senior Notes Repayments

In October 2021, commitments under the Revolving Credit Facility of approximately $76.0 million matured, thereby reducing the remaining commitments outstanding under the Revolving Credit Facility. This maturity, which reduced the remaining credit available under the Revolving Credit Facility, occurred because the 7.25% Senior Notes due 2022 and the 5.75% Senior Notes due 2022 were not refinanced or repaid in full prior to the date that was 91 days prior to their January 15, 2022 maturity dates. As a result of this maturity, the Company repaid approximately $22.8 million of borrowings in October 2021, representing the amount that had been borrowed pursuant to these matured commitments. The 7.25% Senior Notes due 2022 and the 5.75% Senior Notes due 2022 were repaid in January 2022.

Maturities

As noted above, the initiation of our bankruptcy proceedings constituted an event of default that accelerated our obligations under substantially all of our then-outstanding debt instruments. The following table presents, as of December 31, 2022, for each of the five fiscal years subsequent to December 31, 2022, the stated maturities on our long-term debt that would have been applicable if not for such acceleration (in thousands):

	Maturities (1)
2023	$ 82,563
2024 (2)	$ 394,600
2025	$ 41,578
2026 (2)	$ 222,600
2027	$ 2,976,069

(1) The terms of the Credit Agreement provide that certain amounts borrowed pursuant to the Credit Facilities could mature prior to their scheduled maturity date if certain of our senior notes are not refinanced or repaid prior to the date that is 91 days prior to the respective stated maturity dates thereof The amounts in this maturities table do not reflect any potential early repayments or refinancings

(2) Based on the Company's borrowings under the Revolving Credit Facility that were outstanding at December 31, 2022, $74 6 million would have matured in 2024, with the remainder maturing in 2026

As discussed above, as a result of the Chapter 11 Cases, since the Petition Date, we have not made, and we are not currently making, any scheduled principal or interest payments on the Credit Facilities or our various senior notes and senior secured notes. Therefore, the timing and amount of any future principal and interest payments is uncertain. The table above excludes $10.0 million of principal outstanding on our Term Loan Facility that, pursuant to the terms of the Credit Agreement, matured on or before December 31, 2022 but has not yet been paid as a result of the Chapter 11 Cases.

NOTE 16. COMMITMENTS AND CONTINGENCIES

Manufacturing, Supply and Other Service Agreements

Our subsidiaries contract with various third-party manufacturers, suppliers and service providers to provide raw materials used in our subsidiaries' products and semi-finished and finished goods, as well as certain packaging, labeling services, customer service support, warehouse and distribution services. If, for any reason, we are unable to obtain sufficient quantities of any of the finished goods or raw materials or components required for our products or services needed to conduct our business, it could have a material adverse effect on our business, financial condition, results of operations and cash flows.

In addition to the manufacturing and supply agreements described above, we have agreements with various companies for clinical development and certain other services. Although we have no reason to believe that the parties to these agreements will not meet their obligations, failure by any of these third parties to honor their contractual obligations may have a material adverse effect on our business, financial condition, results of operations and cash flows.

U.S. Government Agreement

In November 2021, our PSP LLC subsidiary entered into a cooperative agreement with the U.S. government to expand our Sterile Injectables segment's fill-finish manufacturing production capacity and capabilities at our Rochester, Michigan plant to support the U.S. government's national defense efforts regarding production of critical medicines advancing pandemic preparation (the U.S. Government Agreement). The U.S. Government Agreement is part of the U.S. government's efforts, authorized under the Defense Production Act, to address potential vulnerabilities in critical product supply chains and strengthen the advancement of domestic manufacturing capabilities critical to the national defense, including essential medicines production.

Under the terms of the U.S. Government Agreement, our Rochester facility will establish new sterile fill-finish manufacturing assets capable of processing liquid or lyophilized products requiring Biosafety Level (BSL) 2 containment in order to establish and sustain BSL 2 sterile fill-finish production capacity to create and maintain industrial base capabilities for the national defense. Certain qualifying costs are eligible for reimbursement by the U.S. government under a cost share arrangement, generally within 30 days of us submitting requests for reimbursement. The Company must generally incur the costs before subsequently seeking reimbursement of qualifying costs from the U.S. government. Amounts reimbursed are subject to audit and may be recaptured by the U.S. government in certain circumstances.

Construction is currently in progress. During the year ended December 31, 2022, we incurred approximately $39.0 million of costs associated with the U.S. Government Agreement. Additional information about such costs is included below:

- Approximately $34.9 million has been capitalized and recorded as Property, plant and equipment, net in our Consolidated Balance Sheets as of December 31, 2022. We have also recorded deferred income of approximately $26.5 million, representing the reimbursable portion of the costs incurred, which is included in Other liabilities in our Consolidated Balance Sheets as of December 31, 2022.
- Approximately $1.0 million has been charged to expense during the year ended December 31, 2022, with the majority of such expense included within Selling, general and administrative expenses and Cost of revenues in our Consolidated Statements of Operations. This amount is net of approximately $3.1 million, representing the reimbursable portion of costs incurred.

Amounts included in our Consolidated Financial Statements as of and for the year ended December 31, 2021 were not material.

We currently estimate that between approximately one-quarter and one-third of our expected capital expenditures related to this agreement, as well as the corresponding reimbursements from the U.S. government, have occurred through December 31, 2022. We currently anticipate that facility readiness will occur in 2025, but there can be no assurance this will occur.

The new sterile fill-finish manufacturing assets will be available to support our future commercial operations, subject to the U.S. government's conditional priority access and certain preferred pricing obligations under the U.S. Government Agreement. The U.S. government will have conditional priority access to the facility for an initial period of ten years from the completion of the expansion project, which could be extended in the future after good faith negotiation and on commercially reasonable terms and conditions. Specifically, the U.S. government (or a third-party U.S. government supporting entity) will have priority access to utilize the new sterile fill-finish manufacturing assets for the production of a medical countermeasure if a determination is made in writing by the Secretary of HHS that the priority access is needed to respond to a disease, health condition or other threat to the public health that causes a public health emergency or a credible risk of such an emergency. The U.S. Government Agreement also contemplates the establishment of separate supply agreements to be negotiated in good faith on mutually-acceptable commercially reasonable terms. Refer to Note 3. Summary of Significant Accounting Policies for additional information about our accounting for the U.S. Government Agreement.

Legal Proceedings and Investigations

We and certain of our subsidiaries are involved in various claims, legal proceedings and internal and governmental investigations (collectively, proceedings) arising from time to time, including, among others, those relating to product liability, intellectual property, regulatory compliance, consumer protection, tax and commercial matters. An adverse outcome in certain proceedings described herein could have a material adverse effect on our business, financial condition, results of operations and cash flows. We are also subject to a number of matters that are not being disclosed herein because, in the opinion of our management, these matters are immaterial both individually and in the aggregate with respect to our financial position, results of operations and cash flows.

As further discussed in Note 2. Bankruptcy Proceedings, on the Petition Date, the Debtors filed voluntary petitions for relief under the Bankruptcy Code. Under the Bankruptcy Code, third-party actions to collect pre-petition indebtedness owed by the Debtors, as well as most litigation pending against the Debtors as of the Petition Date, are generally subject to an automatic stay. However, under the Bankruptcy Code, certain legal proceedings, such as those involving the assertion of a governmental entity's police or regulatory powers, may not be subject to the automatic stay and may continue unless otherwise ordered by the Bankruptcy Court. As a result, some proceedings may continue (or certain parties may attempt to argue that such proceedings should continue) notwithstanding the automatic stay. Where no stay is in place or expected, and in the event the stays in place were to be lifted, we intend to vigorously prosecute or defend our position as appropriate. We cannot predict the outcome of any proceeding, and there can be no assurance that we will be successful or obtain any requested relief.

We believe that certain settlements and judgments, as well as legal defense costs, relating to certain product liability or other matters are or may be covered in whole or in part under our insurance policies with a number of insurance carriers. In certain circumstances, insurance carriers reserve their rights to contest or deny coverage. We intend to contest vigorously any disputes with our insurance carriers and to enforce our rights under the terms of our insurance policies. Notwithstanding the foregoing, amounts recovered under our insurance policies could be materially less than stated coverage limits and may not be adequate to cover damages, other relief and/or costs relating to claims. In addition, there is no guarantee that insurers will pay claims in the amounts we expect or that coverage will otherwise be available. Even where claims are submitted to insurance carriers for defense and indemnity, there can be no assurance that the claims will be covered by insurance or that the indemnitors or insurers will remain financially viable or will not challenge our right to reimbursement in whole or in part. Accordingly, we will record receivables with respect to amounts due under these policies only when the realization of the potential claim for recovery is considered probable.

We may not have and may be unable to obtain or maintain insurance on acceptable terms or with adequate coverage against potential liabilities or other losses, including costs, judgments, settlements and other liabilities incurred in connection with current or future legal proceedings, regardless of the success or failure of the claim. For example, we do not have insurance sufficient to satisfy all of the opioid claims that have been made against us. We also generally no longer have product liability insurance to cover claims in connection with the mesh-related litigation described herein. Additionally, we may be limited by the surviving insurance policies of acquired entities, which may not be adequate to cover potential liabilities or other losses. The failure to generate sufficient cash flow or to obtain other financing could affect our ability to pay amounts due under those liabilities not covered by insurance. Additionally, the nature of our business, the legal proceedings to which we are exposed and any losses we suffer may increase the cost of insurance, which could impact our decisions regarding our insurance programs.

As of December 31, 2022, our accrual for loss contingencies totaled $820.8 million, the most significant components of which relate to: (i) various opioid-related matters as further described herein and (ii) product liability and related matters associated with transvaginal surgical mesh products, which we have not sold since March 2016. Although we believe there is a possibility that a loss in excess of the amount recognized exists, we are unable to estimate the possible loss or range of loss in excess of the amount recognized at this time. As of December 31, 2022, our entire accrual for loss contingencies is classified as Liabilities subject to compromise in the Consolidated Balance Sheets. As a result of the automatic stay under the Bankruptcy Code and the uncertain treatment of these liabilities pursuant to a chapter 11 plan or otherwise, the timing and amount of payment, if any, related to the amounts accrued for loss contingencies is uncertain.

As part of the Chapter 11 Cases, persons and entities believing that they have claims or causes of action against the Debtors, including litigants, may file proofs of claim evidencing such claims. While no bar date (deadline) for holders of claims to file proofs of claim has yet been set, the Debtors have filed a motion seeking Bankruptcy Court approval to establish such deadline. The motion has been adjourned to an undetermined date, and as a result, the proposed deadlines set forth in the motion are expected to be extended.

At the Debtors' request, the Bankruptcy Court has appointed a future claims representative (FCR) in the Chapter 11 Cases. As further described in the applicable bankruptcy court filings, the FCR represents the rights of individuals who may in the future assert one or more claims against the Debtors or a successor of the Debtors' businesses for personal injury based on the Debtors' opioid, transvaginal mesh or ranitidine products, but who could not assert such claims in the Chapter 11 Cases because, among other reasons, the claimant was unaware of the alleged injury, had a latent manifestation of the alleged injury or was otherwise unable to assert or incapable of asserting the claims based on the alleged injury.

Vaginal Mesh Matters

Since 2008, we and certain of our subsidiaries, including American Medical Systems Holdings, Inc. (AMS) (which subsequently converted to Astora Women's Health Holdings, LLC and merged into Astora Women's Health LLC (Astora)), have been named as defendants in multiple lawsuits in various state and federal courts in the U.S., and in the United Kingdom, Australia and other countries, alleging personal injury resulting from the use of transvaginal surgical mesh products designed to treat POP and SUI. We have not sold such products since March 2016. Plaintiffs claim a variety of personal injuries, including chronic pain, incontinence, inability to control bowel function and permanent deformities, and seek compensatory and punitive damages, where available.

At various times from June 2013 through the Petition Date, the Company and/or certain of its subsidiaries entered into various Master Settlement Agreements (MSAs) and other agreements intended to resolve approximately 71,000 filed and unfiled U.S. mesh claims. These MSAs and other agreements were solely by way of compromise and settlement and were not an admission of liability or fault by us or any of our subsidiaries. All MSAs have been subject to a process that includes guidelines and procedures for administering the settlements and the release of funds. In certain cases, the MSAs have provided for the creation of QSFs into which settlement funds are deposited, established participation requirements and allowed for a reduction of the total settlement payment in the event participation thresholds are not met. In certain circumstances, participation requirements or other conditions for payment were not satisfied prior to the Petition Date. Funds deposited in QSFs are considered restricted cash and/or restricted cash equivalents. Distribution of funds to any individual claimant is conditioned upon the receipt of documentation substantiating product use, the dismissal of any lawsuit and the release of the claim as to us and all affiliates. Prior to receiving funds, an individual claimant must represent and warrant that liens, assignment rights or other claims identified in the claims administration process have been or will be satisfied by the individual claimant. Confidentiality provisions apply to the settlement funds, amounts allocated to individual claimants and other terms of the agreements.

The following table presents the changes in the mesh-related QSFs and liability accrual balances during the year ended December 31, 2022 (in thousands):

	Mesh Qualified Settlement Funds	Mesh Liability Accrual
Balance as of December 31, 2021	$ 78,402	$ 258,137
Cash received for reversionary interests, net of cash contributions to Qualified Settlement Funds	(367)	—
Cash distributions to settle disputes from Qualified Settlement Funds	(28,159)	(28,159)
Other cash distributions to settle disputes	—	(6,499)
Other (1)	463	(507)
Balance as of December 31, 2022 (2)	$ 50,339	$ 222,972

(1) Amounts deposited in the QSFs earn interest from time to time that is reflected in the table above as an increase to the QSF and Mesh Liability Accrual balances Subject to any restrictions on making payments as a result of the Chapter 11 Cases, such interest is generally used to pay administrative costs of the funds and any interest remaining after all claims have been paid will generally be distributed to the claimants who participated in that settlement Also included within this line are foreign currency adjustments for settlements not denominated in U S dollars

(2) As of December 31, 2022, this balance is classified as Liabilities subject to compromise in the Consolidated Balance Sheets

Charges related to vaginal mesh liability and associated legal fees and other expenses for all periods presented are reported in Discontinued operations, net of tax in our Consolidated Statements of Operations.

As of December 31, 2022, the Company has made total cumulative mesh liability payments of approximately $3.6 billion, $50.3 million of which remains in the QSFs as of December 31, 2022. In light of the filing of petitions for relief under the Bankruptcy Code, we do not expect to make new payments under previously executed mesh settlement agreements within the next 12 months. As funds are disbursed out of the QSFs from time to time, the liability accrual will be reduced accordingly with a corresponding reduction to restricted cash and cash equivalents.

As of the Petition Date, mesh personal injury claims against AMS and Astora became subject to the automatic stay applicable under the Bankruptcy Code, and stays on mesh litigation have been obtained in the United Kingdom and Australia. In certain other countries where no stay is in place, and in the event the stays in place were to be lifted, we will continue to vigorously defend any unresolved claims and to explore other options as appropriate in our best interests.

We were contacted in October 2012 regarding a civil investigation initiated by various U.S. state attorneys general into mesh products, including transvaginal surgical mesh products designed to treat POP and SUI. In November 2013, we received a subpoena relating to this investigation from the state of California, and we subsequently received additional subpoenas from California and other states. We are cooperating with the investigations.

Similar matters may be brought by others or the foregoing matters may be expanded. We are unable to predict the outcome of these matters or to estimate the possible range of any additional losses that could be incurred.

Although the Company believes it has appropriately estimated the probable total amount of loss associated with all mesh-related matters as of the date of this report, it is reasonably possible that adjustments to our overall liability accrual may be required. This could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Opioid-Related Matters

Since 2014, multiple U.S. states as well as other governmental persons or entities and private plaintiffs in the U.S. and Canada have filed suit against us and/or certain of our subsidiaries, including EHSI, EPI, PPI, PPCI, Endo Generics Holdings, Inc. (EGHI), Vintage Pharmaceuticals, LLC, Generics Bidco I, LLC, DAVA Pharmaceuticals, LLC, PSP LLC and in Canada, Paladin and EVL, as well as various other manufacturers, distributors, pharmacies and/or others, asserting claims relating to the defendants' alleged sales, marketing and/or distribution practices with respect to prescription opioid medications, including certain of our products. As of February 27, 2023, pending cases in the U.S. of which we were aware include, but are not limited to, approximately 15 cases filed by or on behalf of states; approximately 2,570 cases filed by counties, cities, Native American tribes and/or other government-related persons or entities; approximately 310 cases filed by hospitals, health systems, unions, health and welfare funds or other third-party payers and approximately 220 cases filed by individuals, including but not limited to legal guardians of children born with neonatal abstinence syndrome. Certain of the U.S. cases are putative class actions. The Canadian cases include an action filed by British Columbia on behalf of a proposed class of all federal, provincial and territorial governments and agencies in Canada that paid healthcare, pharmaceutical and treatment costs related to opioids; an action filed in Alberta on behalf of a proposed class of all local or municipal governments in Canada; an action filed in Saskatchewan on behalf of a proposed class of all First Nations communities and local or municipal governments in Canada; and three additional putative class actions, filed in British Columbia, Ontario and Quebec, seeking relief on behalf of Canadian residents who were prescribed and/or consumed opioid medications.

The complaints in the cases assert a variety of claims, including but not limited to statutory claims asserting violations of public nuisance, consumer protection, unfair trade practices, racketeering, Medicaid fraud and/or drug dealer liability laws and/or common law claims for public nuisance, fraud/misrepresentation, strict liability, negligence and/or unjust enrichment. The claims are generally based on alleged misrepresentations and/or omissions in connection with the sale and marketing of prescription opioid medications and/or alleged failures to take adequate steps to identify and report suspicious orders and to prevent abuse and diversion. Plaintiffs seek various remedies including, without limitation, declaratory and/or injunctive relief; compensatory, punitive and/or treble damages; restitution, disgorgement, civil penalties, abatement, attorneys' fees, costs and/or other relief. The damages sought exceed our applicable insurance.

Many of the U.S. cases have been coordinated in a federal multidistrict litigation (MDL) pending in the U.S. District Court for the Northern District of Ohio; however, in April 2022, the Judicial Panel on Multidistrict Litigation issued an order suggesting that, based on the progress of the MDL, it would no longer transfer new cases filed in or removed to federal court to the MDL. Other cases are pending in various federal or state courts. Following the Petition Date, litigation activity against the Company and its subsidiaries ceased in nearly all pending cases as a result of the automatic stay and a November 2022 preliminary injunction order issued by the Bankruptcy Court. A similar cessation of litigation activity is in place in Canada.

In June 2020, the New York State Department of Financial Services (DFS) commenced an administrative action against the Company, EPI, EHSI, PPI and PPCI alleging violations of the New York Insurance Law and New York Financial Services Law. In July 2021, DFS filed an amended statement of charges. The amended statement of charges alleges that fraudulent or otherwise wrongful conduct in the marketing, sale and/or distribution of opioid medications caused false claims to be submitted to insurers. DFS seeks civil penalties for each allegedly fraudulent prescription as well as injunctive relief. In July 2021, EPI, EHSI, PPI and PPCI, among others, filed a petition in New York state court seeking to prohibit DFS from proceeding with its administrative enforcement action. In December 2021, DFS filed a motion to dismiss that petition, which the court granted in June 2022. The Company's subsidiaries, among others, appealed that ruling in July 2022. Both the appeal and the DFS administrative matter were stayed following commencement of the Chapter 11 Cases.

Between 2019 and the Petition Date, the Company and/or certain of its subsidiaries executed a number of settlement agreements to resolve governmental opioid claims brought by certain states, counties, cities and/or other governmental entities. Certain related developments include but are not limited to the following:

- In September 2019, EPI, EHSI, PPI and PPCI executed a settlement agreement with two Ohio counties providing for payments totaling $10 million and up to $1 million of VASOSTRICT® and/or ADRENALIN®. The settlement amount was paid during the third quarter of 2019.
- In January 2020, EPI and PPI executed a settlement agreement with the state of Oklahoma providing for a payment of $8.75 million. The settlement amount was paid during the first quarter of 2020.
- In August 2021, EPI, EHSI, nine counties in eastern Tennessee, eighteen municipalities within those counties and a minor individual executed a settlement agreement providing for a payment of $35 million. The settlement amount was paid during the third quarter of 2021.
- In September 2021, Endo International plc, EPI, EHSI, PPI and PPCI executed a settlement agreement with the state of New York and two of its counties providing for a payment of $50 million. The settlement amount was paid during the third quarter of 2021.
- In October 2021, EPI and EHSI executed a settlement agreement with the Alabama Attorney General's office intended to resolve opioid-related cases and claims of the state and other Alabama governmental persons and entities in exchange for a total payment of $25 million, subject to certain participation thresholds. The settlement amount was not paid as of the Petition Date and, as a result of the Chapter 11 Cases, it is not known when or if such amount will be paid.

- In December 2021, Endo International plc, EPI, EHSI, PPI and PPCI executed a settlement agreement with the Texas Attorney General's office and four Texas counties intended to resolve opioid-related cases and claims of the state and other Texas governmental persons and entities in exchange for a total payment of $63 million, subject to certain participation thresholds. The settlement amount was deposited into a QSF during the first quarter of 2022.
- In January 2022, EPI and EHSI executed a settlement agreement with the Florida Attorney General's office intended to resolve opioid-related cases and claims of the state and other Florida governmental persons and entities in exchange for a total payment of up to $65 million, subject to certain participation thresholds. The settlement amount was deposited into a QSF during the second quarter of 2022.
- In February 2022, EPI and EHSI executed a settlement agreement with the Louisiana Attorney General's office intended to resolve opioid-related cases and claims of the state and other Louisiana governmental persons and entities in exchange for a total payment of $7.5 million, subject to certain participation thresholds. The settlement amount was not paid as of the Petition Date and, as a result of the Chapter 11 Cases, it is not known when or if such amount will be paid.
- In March 2022, EPI, EHSI and PPI executed a settlement agreement with the West Virginia Attorney General's office intended to resolve opioid-related cases and claims of the state and other West Virginia governmental persons and entities in exchange for a total payment of $26 million, subject to certain participation thresholds. The settlement amount was not paid as of the Petition Date and, as a result of the Chapter 11 Cases, it is not known when or if such amount will be paid.
- In June 2022, EPI and EHSI executed a settlement agreement with the Arkansas Attorney General's office and certain Arkansas local governments intended to resolve opioid-related cases and claims of the state and other Arkansas governmental persons and entities in exchange for a total payment of $9.75 million, subject to certain participation thresholds. With the exception of certain amounts held back pursuant to an MDL common benefit fund order, the settlement amount was paid during the third quarter of 2022.
- In July 2022, EPI and EHSI executed a settlement agreement with the Mississippi Attorney General's office intended to resolve opioid-related cases and claims of the state and other Mississippi governmental persons and entities in exchange for a total payment of $9 million, subject to certain participation thresholds. The settlement amount was not paid as of the Petition Date and, as a result of the Chapter 11 Cases, it is not known when or if such amount will be paid.
- In July 2022, EPI, EHSI, PPI and PPCI executed a settlement agreement with the City and County of San Francisco providing for an initial payment of $5 million and subsequent payments of $500,000 a year over ten years. The settlement amount was not paid as of the Petition Date and, as a result of the Chapter 11 Cases, it is not known when or if such amount will be paid.

While the specific terms of the agreements vary, each agreement was solely by way of compromise and settlement and was not in any way an admission of wrongdoing, fault or liability of any kind by us or any of our subsidiaries. Certain settlement agreements provided for the creation of QSFs, the repayment of some or all of the settlement amount under certain conditions and/or additional payments in the event certain conditions were met. Depending on the terms of the respective agreements, funds deposited in QSFs have been and may continue to be considered restricted cash and/or restricted cash equivalents for a period of time subsequent to the initial funding. Distribution of funds from the QSFs is conditioned upon certain criteria that vary by agreement.

Certain of the settlement agreements described above provide for injunctive relief. The RSA also provides for certain voluntary injunctive terms that bind the Debtors during the course of the bankruptcy proceedings and would apply to any purchaser of our opioid business in conjunction with the bankruptcy proceedings. The Bankruptcy Court also approved certain injunctive terms in connection with its November 2022 preliminary injunction against the continued litigation of opioid actions brought by public plaintiffs.

The Stalking Horse Bid provides for the establishment by the Purchaser of voluntary opioid trusts for the benefit of certain public, tribal and private opioid claimants in exchange for certain releases to be provided to (among others) the Purchaser and Endo International plc, its subsidiaries and affiliated entities and persons. In particular, under the RSA, the trusts would distribute up to a total of $550 million over ten years to eligible claimants that opt into the trust agreements by specified participation deadlines. Under the proposed public claimant opioid trust, states which previously reached settlement agreements and received payments from us may elect to participate in the trust. In doing so, those states would agree to return the amounts previously received, net of the amounts allocated to them in the trust agreement and would receive in return a release from any claim for the return of settlement funds under the applicable section of the Bankruptcy Code. The Company would have no obligation or liability with respect to the voluntary trusts, which would be funded exclusively by the Purchaser. As previously noted, the Stalking Horse Bid is subject to higher or otherwise better bids from other parties and therefore there is no certainty regarding whether the proposed sale transaction to the Purchaser, and the funding of the voluntary opioid trusts by the Purchaser, will actually occur.

Although the proposed voluntary opioid trusts would be funded by the Purchaser, and not by the Company or any of its subsidiaries, we previously concluded that the proposed funding amount in the Stalking Horse Bid represented the best estimate of liability relating to the contingencies associated with various opioid claims against the Company and its subsidiaries. As such, during the third quarter of 2022, we recorded charges of approximately $419 million to adjust our aggregate opioid liability accrual to approximately $550 million based on the terms summarized above. As noted above, the Company and various key stakeholders have been engaged in mediation to attempt to resolve certain critical issues in the Chapter 11 Cases, including objections relating to the Sale. On March 3, 2023, the Debtors announced that, as a result of the mediation process, the Ad Hoc First Lien Group (and Stalking Horse Bidder) had reached certain resolutions in principle with both the unsecured creditors' committee and opioid claimants' committee appointed in the Chapter 11 Cases and certain ad hoc groups of debtholders. These resolutions, which remain subject to definitive documentation, are supported by the Debtors. The resolutions include, among other things, a $34 million increase to the funding amounts for the proposed voluntary private opioid trust. Accordingly, during the fourth quarter of 2022, we recorded additional charges of approximately $34 million to increase our aggregate opioid liability accrual to approximately $584 million. The Company believes this modified proposed funding amount represents the best estimate of liability relating to the contingencies associated with various opioid claims against the Company and its subsidiaries. The mediation remains ongoing and could result in additional terms or transactions in the future that may result in further adjustments to our estimated aggregate opioid liability accrual.

To the extent unresolved, and in the event stays in place were to be lifted, we will continue to vigorously defend the foregoing matters and to explore other options as appropriate in our best interests, which may include entering into settlement negotiations and settlements even in circumstances where we believe we have meritorious defenses. Similar matters may be brought by others or the foregoing matters may be expanded. We are unable to predict the outcome of these matters or to estimate the possible range of any losses that could be incurred. Adjustments to our overall liability accrual may be required in the future, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

In addition to the lawsuits and administrative matters described above, the Company and/or its subsidiaries have received certain subpoenas, civil investigative demands (CIDs) and informal requests for information concerning the sale, marketing and/or distribution of prescription opioid medications, including but not limited to the following:

Various state attorneys general have served subpoenas and/or CIDs on EHSI and/or EPI. Some of these state attorneys general subsequently filed lawsuits against the Company and/or its subsidiaries and/or have indicated their support for the opioid trusts described above. To the extent any state attorney general investigations are continuing, we are cooperating with them.

In January 2018, EPI received a federal grand jury subpoena from the U.S. District Court for the Southern District of Florida seeking documents and information related to OPANA® ER, other oxymorphone products and marketing of opioid medications. We are cooperating with the investigation.

In December 2020, the Company received a subpoena issued by the U.S. Attorney's Office for the Western District of Virginia seeking documents related to McKinsey & Company. The Company received a related subpoena in May 2021, also issued by the U.S. Attorney's Office for the Western District of Virginia. We are cooperating with the investigation.

Similar investigations may be brought by others or the foregoing matters may be expanded or result in litigation. We are unable to predict the outcome of these matters or to estimate the possible range of any losses that could be incurred. Adjustments to our overall liability accrual may be required in the future, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Ranitidine Matters

In June 2020, an MDL pending in the U.S. District Court for the Southern District of Florida, *In re Zantac (Ranitidine) Products Liability Litigation*, was expanded to add PPI and numerous other manufacturers and distributors of generic ranitidine as defendants. The claims are generally based on allegations that under certain conditions the active ingredient in ranitidine medications can break down to form an alleged carcinogen known as N-Nitrosodimethylamine (NDMA). The complaints assert a variety of claims, including but not limited to various product liability, breach of warranty, fraud, negligence, statutory and unjust enrichment claims. Plaintiffs generally seek various remedies including, without limitation, compensatory, punitive and/or treble damages; restitution, disgorgement, civil penalties, abatement, attorneys' fees and costs as well as injunctive and/or other relief. Similar complaints against various defendants, in some instances including PPI, have also been filed in certain state courts, including but not limited to California, Illinois and Pennsylvania. Neither PPI nor its subsidiaries have manufactured or sold ranitidine since 2016.

The MDL court has issued various case management orders, including orders directing the filing of "master" and short-form complaints, establishing a census registry process for potential claimants and addressing various discovery issues. In December 2020, the court dismissed the master complaints as to PPI and other defendants with leave to amend certain claims. Certain plaintiffs, including third-party payers pursuing class action claims, appealed the dismissal orders to the U.S. Court of Appeals for the Eleventh Circuit. In February 2021, various other plaintiffs filed an amended master personal injury complaint, a consolidated amended consumer economic loss class action complaint and a consolidated medical monitoring class action complaint. PPI was not named as a defendant in the consumer economic loss complaint or the medical monitoring complaint. In July 2021, the MDL court dismissed all claims in the master complaints as to PPI and other generic defendants with prejudice on federal preemption grounds. In November 2021, the MDL court issued a final judgment as to PPI and other generic defendants. Certain MDL plaintiffs appealed the July 2021 dismissal order and/or the November 2021 judgment. In December 2022, the MDL court granted summary judgment in favor of the remaining branded manufacturer defendants, holding that plaintiffs had failed to provide sufficient evidence of causation.

In July 2022, claimants who alleged certain types of injuries were "exited" from the MDL census registry. Some of these claimants subsequently filed lawsuits in various courts.

As of the Petition Date, the claims against PPI became subject to the automatic stay. Thereafter, PPI was voluntarily dismissed from several pending matters, including the appeal from the MDL court's dismissal of the third-party payer class action complaint.

In the event the stays in place were to be lifted, we will continue to vigorously defend the foregoing matters and to explore other options as appropriate in our best interests. Similar matters may be brought by others or the foregoing matters may be expanded. We are unable to predict the outcome of these matters or to estimate the possible range of any losses that could be incurred. Adjustments to our overall liability accrual may be required in the future, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Generic Drug Pricing Matters

Since March 2016, various private plaintiffs, state attorneys general and other governmental entities have filed cases against our subsidiary PPI and/or, in some instances, the Company, Generics Bidco I, LLC, DAVA Pharmaceuticals, LLC, DAVA International, LLC, EPI, EHSI and/or PPCI, as well as other pharmaceutical manufacturers and, in some instances, other corporate and/or individual defendants, alleging price-fixing and other anticompetitive conduct with respect to generic pharmaceutical products. These cases, which include proposed class actions filed on behalf of direct purchasers, end-payers and indirect purchaser resellers, as well as non-class action suits, have generally been consolidated and/or coordinated for pretrial proceedings in a federal MDL pending in the U.S. District Court for the Eastern District of Pennsylvania; three cases commenced by writ of summons in Pennsylvania state court are in deferred status. There is also a proposed class action filed in the Federal Court of Canada on behalf of a proposed class of Canadian purchasers.

The various complaints and amended complaints generally assert claims under federal and/or state antitrust law, state consumer protection statutes and/or state common law, and generally seek damages, treble damages, civil penalties, disgorgement, declaratory and injunctive relief, costs and attorneys' fees. Some claims are based on alleged product-specific conspiracies; other claims allege broader, multiple-product conspiracies. Under their overarching conspiracy theories, plaintiffs generally seek to hold all alleged participants in a particular conspiracy jointly and severally liable for all harms caused by the alleged conspiracy, not just harms related to the products manufactured and/or sold by a particular defendant.

The MDL court has issued various case management and substantive orders, including orders denying certain motions to dismiss in whole or in part, and discovery is ongoing.

As of the Petition Date, the claims against the Company and its subsidiaries in the U.S. became subject to the automatic stay. A similar cessation of litigation activity is in place in Canada. In the event the stays in place were to be lifted, we will continue to vigorously defend the foregoing matters and to explore other options as appropriate in our best interests. Similar matters may be brought by others or the foregoing matters may be expanded. We are unable to predict the outcome of these matters or to estimate the possible range of any losses that could be incurred. Adjustments to our overall liability accrual may be required in the future, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

In December 2014, our subsidiary PPI received from the Antitrust Division of the DOJ a federal grand jury subpoena issued by the U.S. District Court for the Eastern District of Pennsylvania addressed to "Par Pharmaceuticals." The subpoena requested documents and information focused primarily on product and pricing information relating to the authorized generic version of Lanoxin® (digoxin) oral tablets and generic doxycycline products, and on communications with competitors and others regarding those products. We are cooperating with the investigation.

In May 2018, we and our subsidiary PPCI each received a CID from the DOJ in relation to an FCA investigation concerning whether generic pharmaceutical manufacturers engaged in price-fixing and market allocation agreements, paid illegal remuneration and caused the submission of false claims. We are cooperating with the investigation.

Similar investigations may be brought by others or the foregoing matters may be expanded or result in litigation. We are unable to predict the outcome of these matters or to estimate the possible range of any losses that could be incurred. Adjustments to our overall liability accrual may be required in the future, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Other Antitrust Matters

Beginning in June 2014, multiple alleged purchasers of OPANA® ER sued our subsidiaries EHSI and EPI; Penwest Pharmaceuticals Co. (Penwest), which our subsidiary EPI had acquired; and Impax Laboratories, LLC (formerly Impax Laboratories, Inc. and referred to herein as Impax), alleging among other things violations of antitrust law arising out of an agreement between EPI and Impax to settle certain patent infringement litigation. Some cases were filed on behalf of putative classes of direct and indirect purchasers; others were non-class action suits. The cases were consolidated and/or coordinated in a federal MDL pending in the U.S. District Court for the Northern District of Illinois. The various complaints asserted claims under Sections 1 and 2 of the Sherman Act, state antitrust and consumer protection statutes and/or state common law. Plaintiffs generally sought damages, treble damages, disgorgement of profits, restitution, injunctive relief and attorneys' fees. In June 2021, the court certified a direct purchaser class and an end-payer class; in August 2021, following an appeal, the district court amended its class certification order to certify a narrower end-payer class. Trial on all plaintiffs' claims began in June 2022. In July 2022, the jury returned a verdict in favor of EHSI, EPI and Penwest (Impax settled during trial). Later that month, plaintiffs filed a motion for judgment as a matter of law or in the alternative for a new trial. As of the Petition Date, the matter became subject to the automatic stay.

Beginning in February 2009, the FTC and certain private plaintiffs sued our subsidiaries PPCI (since June 2016, EGHI) and/or PPI as well as other pharmaceutical companies alleging violations of antitrust law arising out of the settlement of certain patent litigation concerning the generic version of AndroGel® and seeking damages, treble damages, equitable relief and attorneys' fees and costs. The cases were consolidated and/or coordinated for pretrial proceedings in a federal MDL pending in the U.S. District Court for the Northern District of Georgia. In May 2016, plaintiffs representing a putative class of indirect purchasers voluntarily dismissed their claims with prejudice. In February 2017, the FTC voluntarily dismissed its claims against EGHI with prejudice. In June 2018, the MDL court granted in part and denied in part various summary judgment and evidentiary motions filed by defendants. In particular, among other things, the court rejected two of the remaining plaintiffs' causation theories and rejected damages claims related to AndroGel® 1.62%. In July 2018, the court denied certain plaintiffs' motion for certification of a direct purchaser class. Between November 2019 and April 2021, PPI and PPCI entered into settlement agreements with all of the plaintiffs remaining in the MDL. The settlement agreements were solely by way of compromise and settlement and were not in any way an admission of wrongdoing, fault or liability of any kind. Separately, in August 2019, several alleged direct purchasers filed suit against PPI and other pharmaceutical companies in the U.S. District Court for the Eastern District of Pennsylvania asserting claims substantially similar to those asserted in the MDL, as well as additional claims against other defendants relating to other alleged conduct. As of the Petition Date, the claims against PPI became subject to the automatic stay.

Beginning in May 2018, multiple complaints were filed in the U.S. District Court for the Southern District of New York against PPI, EPI and/or us, as well as other pharmaceutical companies, alleging violations of antitrust law arising out of the settlement of certain patent litigation concerning the generic version of Exforge® (amlodipine/valsartan). Some cases were filed on behalf of putative classes of direct and indirect purchasers; others are non-class action suits. The various complaints assert claims under Sections 1 and 2 of the Sherman Act, state antitrust and consumer protection statutes and/or state common law. Plaintiffs generally seek damages, treble damages, equitable relief and attorneys' fees and costs. In September 2018, the putative class plaintiffs stipulated to the dismissal without prejudice of their claims against EPI and us; the retailer plaintiffs later did the same. PPI filed a partial motion to dismiss certain claims in September 2018; the court granted the motion in August 2019. In March 2022, the putative class plaintiffs filed motions for class certification. In May 2022, defendants filed motions for summary judgment. As of the Petition Date, the claims against PPI became subject to the automatic stay. In January 2023, certain direct purchaser plaintiffs dismissed their claims against PPI, EPI and us with prejudice and, in February 2023, certain indirect purchaser plaintiffs agreed to do the same.

Beginning in August 2019, multiple complaints were filed in the U.S. District Court for the Southern District of New York against PPI and other pharmaceutical companies alleging violations of antitrust law arising out the settlement of certain patent litigation concerning generic versions of Seroquel XR® (extended-release quetiapine fumarate). The claims against PPI are based on allegations that PPI entered into an exclusive acquisition and license agreement with Handa Pharmaceuticals, LLC (Handa) in 2012 pursuant to which Handa assigned to PPI certain rights under a prior settlement agreement between Handa and AstraZeneca resolving certain patent litigation. Some cases were filed on behalf of putative classes of direct and indirect purchasers; others are non-class action suits. The various complaints assert claims under Sections 1 and 2 of the Sherman Act, state antitrust and consumer protection statutes and/or state common law. Plaintiffs generally seek damages, treble damages, equitable relief and attorneys' fees and costs. In August 2020, the litigation was transferred to the U.S. District Court for the District of Delaware. In July 2022, the court dismissed certain claims asserted under state law but otherwise denied defendants' motions to dismiss. As of the Petition Date, the claims against PPI became subject to the automatic stay.

Beginning in June 2020, multiple complaints were filed against Jazz Pharmaceuticals and other pharmaceutical companies, including PPI, alleging violations of state and/or federal antitrust laws in connection with the settlement of certain patent litigation concerning generic versions of Xyrem® (sodium oxybate). Some cases were filed on behalf of putative classes of indirect purchasers; others are non-class action suits. The cases have generally been consolidated and/or coordinated for pretrial proceedings in a federal MDL pending in the U.S. District Court for the Northern District of California; Aetna Inc. filed a similar case in May 2022 in California state court. The various complaints allege that Jazz entered into a series of "reverse-payment" settlements, including with PPI, to delay generic competition for Xyrem® and assert claims under Sections 1 and 2 of the Sherman Act, Section 16 of the Clayton Act, state antitrust and consumer protection statutes and/or state common law. Plaintiffs generally seek damages, treble damages, equitable relief and attorneys' fees and costs. In April 2021, the defendants moved to dismiss the MDL complaints that had been filed as of that time. In August 2021, the MDL court issued an order dismissing certain aspects of the plaintiffs' claims but otherwise denying the motions to dismiss. In July 2022, PPI, among others, filed a motion to quash the Aetna action for lack of personal jurisdiction; the defendants also filed a demurrer, motion to strike and motion to stay Aetna's action. As of the Petition Date, the claims against PPI became subject to the automatic stay. In December 2022, the California state court overseeing the Aetna action granted the motion to quash for lack of personal jurisdiction and, in January 2023, Aetna filed an amended complaint that did not name PPI as a defendant.

In January 2021, the FTC filed a lawsuit in the U.S. District Court for the District of Columbia against us, EPI, Impax Laboratories, LLC and Amneal Pharmaceuticals, Inc., generally alleging that the 2017 settlement of a contract dispute between EPI and Impax (now Amneal) constituted unfair competition in violation of Section 5(a) of the FTC Act. The complaint generally sought injunctive and equitable monetary relief. In April 2021, the defendants filed motions to dismiss, which the court granted in March 2022. The FTC filed a notice of appeal in May 2022. Briefing on the appeal has not been stayed and is expected to conclude in April 2023.

To the extent unresolved, and in the event the stays in place were to be lifted, we will continue to vigorously defend the foregoing matters and to explore other options as appropriate in our best interests. Similar matters may be brought by others or the foregoing matters may be expanded. We are unable to predict the outcome of these matters or to estimate the possible range of any losses that could be incurred. Adjustments to our overall liability accrual may be required in the future, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Securities Litigation

In June 2020, a putative class action entitled *Benoit Albiges v. Endo International plc, Paul V. Campanelli, Blaise Coleman, and Mark T. Bradley* was filed in the U.S. District Court for the District of New Jersey by an individual shareholder on behalf of himself and all similarly situated shareholders. The lawsuit alleged violations of Section 10(b) and 20(a) of the Exchange Act and Rule 10b-5 promulgated thereunder relating to the marketing and sale of opioid medications and DFS's administrative action against the Company, EPI, EHSI, PPI and PPCI. In September 2020, the court appointed Curtis Laakso lead plaintiff in the action. In November 2020, the plaintiffs filed an amended complaint that among other things added Matthew J. Maletta as a defendant. In January 2021, the defendants filed a motion to dismiss, which the court granted in August 2021. In November 2021, the plaintiffs filed a second amended complaint, which among other things added allegations about discovery issues in certain opioid-related lawsuits. In January 2022, the defendants moved to dismiss the second amended complaint. As of the Petition Date, the claims against the Company became subject to the automatic stay. In August 2022, the court granted the motion and dismissed the case with prejudice. The automatic stay does not apply to the individual defendants, and the plaintiffs' time to appeal the ruling as to those defendants has run.

Similar matters may be brought by others. We are unable to predict the outcome of any such matters or to estimate the possible range of any losses that could be incurred. Adjustments to our overall liability accrual may be required in the future, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Miscellaneous Government Investigations

In March 2022, EPI received a CID from the Texas Attorney General's office seeking documents and information related to hormone blocker products. This followed the Texas Attorney General's December 2021 announcement of an investigation into whether EPI and AbbVie Inc. had advertised or promoted such products, including SUPPRELIN® LA and VANTAS®, for unapproved uses. We are cooperating with the investigation.

Similar investigations may be brought by others or the foregoing matter may be expanded or result in litigation. We are unable to predict the outcome of this matter or to estimate the possible range of any losses that could be incurred. Adjustments to our overall liability accrual may be required in the future, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Patent Matters

Beginning in April 2018, PSP LLC and PPI received notice letters from Eagle and other companies advising of the filing by such companies of ANDAs/NDAs for generic versions of VASOSTRICT® (vasopressin IV solution (infusion)) 20 units/ml and/or 200 units/10 ml. Beginning in May 2018, PSP LLC, PPI and EPIC filed lawsuits against Eagle and other generic filers in the U.S. District Court for the District of Delaware or New Jersey. We reached settlements and voluntarily dismissed the suits against many of these filers. The remaining Delaware cases against Eagle and Amneal Pharmaceuticals LLC were consolidated and a trial was held in July 2021. In August 2021, the court issued an opinion holding that Eagle's proposed generic product would not infringe PPI's asserted patent claims. The court made no finding regarding the validity of the patents. We appealed the ruling. In August 2022, the Federal Circuit affirmed the District of Delaware's decision: (i) that Eagle's proposed generic product would not infringe PPI's asserted patent claims and (ii) denying the issuance of a declaratory judgment that Eagle's planned sale of generic product would infringe under 35 U.S.C. § 271(a) and (b).

During the first quarter of 2022, multiple competitive generic alternatives to VASOSTRICT® 20 units/ml were launched, beginning with Eagle's generic that was launched at risk and began shipping toward the end of January 2022. Since then, additional competitive alternatives entered the market, including authorized generics. These launches began to significantly impact both Endo's market share and product price toward the middle of the first quarter of 2022, and the effects of competition have since increased. This competition could have a material adverse effect on our business, financial condition, results of operations and cash flows.

In March 2022, PSP LLC, PPI and EPIC received a notice letter from Cipla Limited (Cipla) advising of its filing of an ANDA for generic versions of VASOSTRICT® (vasopressin injection) for IV use 40 units/100 ml and 60 units/100 ml. In May 2022, PSP LLC and PPI filed a complaint against Cipla in the U.S. District Court for the District of New Jersey, which triggered a 30-month stay of FDA approval of Cipla's ANDA; that stay expires in September 2024. In January 2023, PSP LLC, PPI and EPIC received another notice letter from Cipla advising of its ANDA filing for a generic version of VASOSTRICT® (vasopressin injection) for IV use 20 units/100 ml. In February 2023, PSP LLC and PPI filed a complaint against Cipla concerning this ANDA in the U.S. District Court for the District of New Jersey. The 30-month stay on FDA approval of Cipla's 20 units/100 ml ANDA expires in July 2025.

In January 2023, PSP LLC, PPI and EPIC received a notice letter from Baxter Healthcare Corporation pursuant to 505(b)(3)(B)-(D) of the FFDCA of its NDA submitted under 21 U.S.C. §355(b)(2) seeking FDA approval for vasopressin injection products in 20 units/100 ml and 40 units/100 ml strengths.

Other Proceedings and Investigations

Proceedings similar to those described above may also be brought in the future. Additionally, we are involved in, or have been involved in, arbitrations or various other proceedings that arise in the normal course of our business. We cannot predict the timing or outcome of these other proceedings. Currently, neither we nor our subsidiaries are involved in any other proceedings that we expect to have a material effect on our business, financial condition, results of operations and cash flows.

NOTE 17. OTHER COMPREHENSIVE (LOSS) INCOME

During the years ended December 31, 2022, 2021 and 2020, there were no tax effects allocated to any component of Other comprehensive (loss) income and there were no reclassifications out of Accumulated other comprehensive loss. Substantially all of the Company's Accumulated other comprehensive loss balances at December 31, 2022 and December 31, 2021 consist of Foreign currency translation loss.

NOTE 18. SHAREHOLDERS' DEFICIT

The Company has issued 4,000,000 euro deferred shares of $0.01 each at par. The euro deferred shares are held by nominees in order to satisfy an Irish legislative requirement to maintain a minimum level of issued share capital denominated in euro and to have at least seven registered shareholders. The euro deferred shares carry no voting rights and are not entitled to receive any dividend or distribution.

Share Repurchase Program

Pursuant to Article 11 of the Company's Articles of Association, the Company has broad shareholder authority to conduct ordinary share repurchases by way of redemptions. The Company's authority to repurchase ordinary shares is subject to legal limitations, including restrictions imposed by the Bankruptcy Code and related rules and guidelines during the pendency of the Chapter 11 Cases, and the existence of sufficient distributable reserves. For example, the Companies Act requires Irish companies to have distributable reserves equal to or greater than the amount of any proposed ordinary share repurchase amount. In addition, our existing debt instruments restrict or prevent us from conducting ordinary share repurchases. Agreements governing any future indebtedness, in addition to those governing our current indebtedness, may not permit us to conduct ordinary share repurchases. Unless we are able to generate sufficient distributable reserves or create distributable reserves by reducing our share premium account, we will not be able to repurchase our ordinary shares. As permitted by Irish Law and the Company's Articles of Association, any ordinary shares redeemed shall be cancelled upon redemption.

The Board has approved the 2015 Share Buyback Program that authorizes the Company to redeem, in the aggregate, $2.5 billion of its outstanding ordinary shares. To date, the Company has redeemed and cancelled approximately 4.4 million of its ordinary shares under the 2015 Share Buyback Program for $250.0 million, not including related fees.

NOTE 19. SHARE-BASED COMPENSATION

Stock Incentive Plans

In June 2015, the Company's shareholders approved the 2015 Stock Incentive Plan (the 2015 Plan), which has subsequently been amended, as approved by the Company's shareholders, on multiple occasions. Under the 2015 Plan, stock options (including incentive stock options), stock appreciation rights, restricted stock awards, performance awards and other share- or cash-based awards may be issued at the discretion of the Compensation & Human Capital Committee of the Board from time to time. No ordinary shares are to be granted under previously approved plans, including the Company's 2000, 2004, 2007, 2010 and Assumed Stock Incentive Plans. Any awards previously granted and outstanding under these prior plans remain subject to the terms of those prior plans.

At December 31, 2022, approximately 11.4 million ordinary shares were reserved for future grants under the 2015 Plan. As of December 31, 2022, stock options, restricted stock awards, PSUs, RSUs, long-term cash incentive awards and certain other cash-based awards have been granted under the stock incentive plans.

In February 2023, the Company filed post-effective amendments to its Form S-8 registration statements with respect to the 2015 Plan in order to deregister all remaining unissued securities.

Generally, the grant-date fair value of each award is recognized as expense over the requisite service period. However, expense recognition differs in the case of certain PSUs where the ultimate payout is performance-based. For these awards, at each reporting period, the Company generally estimates the ultimate payout and adjusts the cumulative expense based on its estimate and the percent of the requisite service period that has elapsed.

Presented below are the components of total share-based compensation as recorded in our Consolidated Statements of Operations for the years ended December 31, 2022, 2021 and 2020 (in thousands).

	2022	2021	2020
Selling, general and administrative expenses	$ 16,019	$ 23,400	$ 32,368
Research and development expenses	1,059	1,378	2,504
Cost of revenues	1,136	5,268	6,485
Total share-based compensation expense	$ 18,214	$ 30,046	$ 41,357

As of December 31, 2022, the total remaining unrecognized compensation cost related to non-vested share-based compensation awards for which a grant date has been established as of December 31, 2022 amounted to $10.1 million.

Stock Options

From time to time, the Company grants stock options to its employees as part of their annual share compensation awards and, in certain circumstances, on an ad hoc basis or upon their commencement of service with the Company.

Although we have not granted employee stock options since 2018, previous grants have generally vested ratably, in equal amounts, over a three or four-year service period. As of December 31, 2022, stock options outstanding generally had expiration dates that extended ten years from the respective grant dates.

We estimate the fair value of stock option grants at the date of grant using the Black-Scholes option-pricing model. This model utilizes assumptions related to volatility, the risk-free interest rate, the dividend yield (which is assumed to be zero as the Company has not paid cash dividends to date and does not currently expect to pay cash dividends) and the expected term of the option. Expected volatilities utilized in the model are based mainly on the historical volatility of the Company's share price over a period commensurate with the expected life of the share option as well as other factors. The risk-free interest rate is derived from the U.S. Treasury yield curve in effect at the time of grant. We estimate the expected term of options granted based on our historical experience with our employees' exercise of stock options and other factors.

A summary of the activity for each of the years ended December 31, 2022, 2021 and 2020 is presented below:

	Number of Shares	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term	Aggregate Intrinsic Value (1)
Outstanding as of December 31, 2019	7,280,539	$ 18.93		
Forfeited	(16,953)	$ 11.81		
Expired	(347,000)	$ 35.56		
Outstanding as of December 31, 2020	6,916,586	$ 18.11		
Exercised	(82,331)	$ 7.55		
Forfeited	(11,887)	$ 13.19		
Expired	(438,454)	$ 40.76		
Outstanding as of December 31, 2021	6,383,914	$ 16.70		
Expired	(1,304,602)	$ 20.04		
Outstanding as of December 31, 2022 (2)	5,079,312	$ 15.84	2.01	$ —
Vested and expected to vest as of December 31, 2022 (2)	5,079,312	$ 15.84	2.01	$ —
Exercisable as of December 31, 2022 (2)	5,079,312	$ 15.84	2.01	$ —

(1) The intrinsic value of a stock option is the excess, if any, of the closing price of the Company's ordinary shares on the last trading day of the fiscal year over the exercise price The aggregate intrinsic values presented in the table above represent sum of the intrinsic values of all corresponding stock options that are "in-the-money," if any

(2) On March 3, 2023, the Bankruptcy Court entered orders authorizing the Company to reject outstanding stock option agreements, restricted stock award agreements and performance award agreements

The range of exercise prices for the above stock options outstanding at December 31, 2022 is from $7.55 to $86.54.

The total intrinsic value of options exercised during the year ended December 31, 2021 was $0.1 million. There were no material tax benefits from stock option exercises realized during any of the periods presented above.

Restricted Stock Units and Performance Share Units

From time to time, the Company grants RSUs and PSUs to its employees as part of their annual share compensation awards and, in certain circumstances, on an ad hoc basis or upon their commencement of service with the Company.

As of December 31, 2022: (i) unvested RSUs were subject to three-year vesting periods, with ratable vesting on the first, second and third anniversaries of the respective grant dates, and (ii) unvested PSUs were subject to three-year service periods, after which the awards would vest in full (conditioned upon the achievement of performance and/or market conditions established by the Compensation & Human Capital Committee of the Board and certain continued employment conditions), with the actual number of shares awarded adjusted to between zero and 200% of the target award amount based upon the level of achievement of the performance criteria described below.

No PSUs were awarded in 2022. PSUs awarded in 2021 and 2020 were based upon two discrete measures: relative total shareholder return (TSR) and an adjusted free cash flow performance metric (FCF), each accounting for 50% of the PSUs upon issuance, with TSR performance being measured against the three-year TSR of a custom index of companies and FCF performance being measured against a target covering a three-year performance period. TSR is considered a market condition under applicable authoritative guidance, while FCF is considered performance condition.

RSUs are valued based on the closing price of Endo's ordinary shares on the date of grant. PSUs with TSR conditions are valued using a Monte-Carlo variant valuation model, while those with FCF conditions are valued taking into consideration the probability of achieving the specified performance goal. The Monte-Carlo variant valuation model used considers a variety of potential future share prices for Endo as well as our peer companies in a selected market index.

A summary of our non-vested RSUs and PSUs for the years ended December 31, 2022, 2021 and 2020 is presented below:

	Number of Shares	Aggregate Intrinsic Value (1)
Non-vested as of December 31, 2019	12,916,289	
Granted	3,761,648	
Forfeited	(824,299)	
Vested	(5,513,359)	
Non-vested as of December 31, 2020	10,340,279	
Granted	4,483,385	
Forfeited	(1,302,292)	
Vested	(5,380,262)	
Non-vested as of December 31, 2021	8,141,110	
Granted	280,373	
Forfeited	(1,116,960)	
Vested	(2,324,696)	
Non-vested as of December 31, 2022 (2)	4,979,827	$ 348,588
Vested and expected to vest as of December 31, 2022 (2)	4,751,674	$ 332,617

(1) The aggregate intrinsic values presented in the table above were calculated by multiplying the closing price of the Company's ordinary shares on the last trading day of the fiscal year by the corresponding quantities above

(2) On March 3, 2023, the Bankruptcy Court entered orders authorizing the Company to reject outstanding stock option agreements, restricted stock award agreements and performance award agreements In connection with the rejection of these agreements, the Company currently expects to recognize any remaining unrecognized compensation cost associated with these agreements during the first quarter of 2023

As of December 31, 2022, the weighted average remaining requisite service period of the units presented in the table above was 0.8 years and the corresponding total remaining unrecognized compensation cost amounted to $3.5 million in the case of RSUs and $6.6 million in the case of PSUs.

The weighted average grant-date fair value of the units granted during the years ended December 31, 2022, 2021 and 2020 was $3.21, $7.39 and $5.54 per unit, respectively.

NOTE 20. OTHER INCOME, NET

The components of Other income, net for the years ended December 31, 2022, 2021 and 2020 are as follows (in thousands):

	2022	2021	2020
Net gain on sale of business and other assets (1)	$ (26,183)	$ (4,516)	$ (16,353)
Foreign currency (gain) loss, net (2)	(2,087)	1,253	2,466
Net loss (gain) from our investments in the equity of other companies (3)	378	453	(2,160)
Other miscellaneous, net (4)	(6,162)	(16,964)	(5,063)
Other income, net	$ (34,054)	$ (19,774)	$ (21,110)

(1) Amounts primarily relate to the sales of certain intellectual property rights and certain other assets including, in 2022 and 2021, assets associated with the sale transactions that are further discussed in Note 4 Discontinued Operations and Asset Sales

(2) Amounts relate to the remeasurement of the Company's foreign currency denominated assets and liabilities

(3) Amounts relate to the income statement impacts of our investments in the equity of other companies, including investments accounted for under the equity method

(4) Amounts in 2021 include gains of $15 5 million associated with the termination of certain contracts

NOTE 21. INCOME TAXES

Loss from Continuing Operations before Income Tax

Our operations are conducted through our various subsidiaries in numerous jurisdictions throughout the world. We have provided for income taxes based upon the tax laws and rates in the jurisdictions in which our operations are conducted.

The components of our Loss from continuing operations before income tax by geography for the years ended December 31, 2022, 2021 and 2020 are as follows (in thousands):

	2022	2021	2020
U.S.	$ (2,429,315)	$ 4,792,852	$ (375,262)
International	(458,787)	(5,339,455)	348,744
Total loss from continuing operations before income tax	$ (2,888,102)	$ (546,603)	$ (26,518)

Income tax from continuing operations consists of the following for the years ended December 31, 2022, 2021 and 2020 (in thousands):

	2022	2021	2020
Current:			
U.S. Federal	$ 21,057	$ 13,649	$ (108,866)
U.S. State	1,731	1,491	(434)
International	6,031	10,495	(1,124)
Total current income tax	$ 28,819	$ 25,635	$ (110,424)
Deferred:			
U.S. Federal	$ (622)	$ 118	$ (143,411)
U.S. State	1,065	(564)	(11,773)
International	(7,746)	(2,711)	(8,374)
Total deferred income tax	$ (7,303)	$ (3,157)	$ (163,558)
Total income tax	$ 21,516	$ 22,478	$ (273,982)

Tax Rate

A reconciliation of income tax from continuing operations at the U.S. federal statutory income tax rate to the total income tax provision from continuing operations for the years ended December 31, 2022, 2021 and 2020 is as follows (in thousands):

	2022	2021	2020
Notional U.S. federal income tax provision at the statutory rate	$ (606,502)	$ (114,787)	$ (5,569)
State income tax, net of federal benefit	(9,517)	6,750	(17,311)
U.S. tax reform impact	—	—	(129,599)
Uncertain tax positions	21,930	42,415	35,941
Residual tax on non-U.S. net earnings	(32,257)	(181,739)	(83,550)
Non-deductible goodwill impairment	385,459	76,230	7,490
Change in valuation allowance	306,497	495,565	(97,752)
Base erosion minimum tax	—	—	77,438
Non-deductible expenses	47,221	39,791	8,875
Executive compensation limitation	5,580	6,215	5,857
Equity based compensation	3,247	2,695	6,495
Financing activities (1)	73,629	(287,012)	(33,217)
Investment activities (2)	(178,018)	(68,943)	(44,964)
Other	4,247	5,298	(4,116)
Income tax	$ 21,516	$ 22,478	$ (273,982)

(1) The amount in 2022 primarily relates to non-deductible foreign currency adjustments on intercompany debt The amount in 2021 primarily relates to a net tax benefit of approximately $1 2 billion related to non-taxable intercompany cancellation of indebtedness income, which was partially offset by a net tax expense of approximately $465 million related to non-deductible bad debt expense and a net tax expense of approximately $427 million related to non-deductible intercompany interest expense The net tax benefit is fully offset by an increase to the valuation allowance

(2) The amounts in 2022 and 2021 primarily relate to tax deductible losses associated with the investment in consolidated subsidiaries The tax benefit is fully offset by an increase to the valuation allowance

The change in income tax expense in 2022 compared to the 2021 income tax expense primarily relates to an increase in accrued interest on uncertain tax positions and changes in the geographic mix of pre-tax earnings. The change in income tax expense in 2021 compared to the 2020 income tax benefit primarily relates to the 2020 tax benefit for the CARES Act as discussed in more detail below and changes in deferred tax liabilities following the BioSpecifics acquisition during 2020.

On March 27, 2020, the CARES Act was enacted by the U.S. government in response to the COVID-19 pandemic. The CARES Act, among other things, permits NOL carryovers and carrybacks to offset 100% of taxable income for taxable years beginning before 2021. In addition, the CARES Act allows NOLs incurred in 2018, 2019 and 2020 to be carried back to each of the five preceding taxable years to generate a refund of previously paid income taxes. During the year ended December 31, 2020, the Company recorded a discrete tax benefit in continuing operations of $129.6 million as a result of the change in the NOL carryback period.

Deferred Tax Assets and Liabilities

Deferred income taxes result from temporary differences between the amount of assets and liabilities recognized for financial reporting and tax purposes. The significant components of the net deferred income tax liability shown on the balance sheets as of December 31, 2022 and 2021 are as follows (in thousands):

	December 31, 2022	December 31, 2021
Deferred tax assets:		
Accrued expenses and reserves	$ 220,415	$ 144,573
Deferred interest deduction	421,552	347,501
Fixed assets, intangible assets and deferred amortization	560,257	512,584
Loss on capital assets	23,511	64,503
Net operating loss carryforward	9,214,688	9,258,122
Other	49,943	50,694
Research and development and other tax credit carryforwards	7,777	8,254
Total gross deferred income tax assets	$ 10,498,143	$ 10,386,231
Deferred tax liabilities:		
Other	$ (3,156)	$ (8,586)
Investments	(107)	(124,311)
Intercompany notes	(72,286)	(104,530)
Total gross deferred income tax liabilities	$ (75,549)	$ (237,427)
Valuation allowance	(10,436,419)	(10,169,294)
Net deferred income tax liability	$ (13,825)	$ (20,490)

As of December 31, 2022, the Company had significant deferred tax assets for tax credits, net operating and capital loss carryforwards, net of unrecognized tax positions, as presented below (in thousands):

Jurisdiction	Amount	Begin to Expire
Ireland	$ 79,617	Indefinite
Luxembourg	$ 8,934,046	2034
U.S.:		
Federal-ordinary losses	$ 19,105	2037
Federal-capital losses	$ 13,699	2023
Federal-tax credits	$ 14,081	2025
State-ordinary losses	$ 227,587	2023
State-capital losses	$ 11,871	2023
State-tax credits	$ 3,256	2037

A valuation allowance is required when it is more likely than not that all or a portion of a deferred tax asset will not be realized. The Company assesses the available positive and negative evidence to estimate whether the existing deferred tax assets will be realized.

The Company has recorded a valuation allowance against certain jurisdictional NOL carryforwards and other tax attributes. As of December 31, 2022 and 2021, the total valuation allowance was $10,436.4 million and $10,169.3 million, respectively. During the years ended December 31, 2022 and 2021, the Company increased its valuation allowance by $267.1 million and $500.7 million, respectively, which was primarily driven by taxable losses in Luxembourg related to investments in consolidated subsidiaries. As previously disclosed, the Company concluded that there was substantial doubt about its ability to continue as a going concern within one year after the date of issuance of the Condensed Consolidated Financial Statements included in the Second-Quarter 2022 Form 10-Q. The Company considered this in determining that certain net deferred tax assets were no longer more likely than not realizable. As a result, an immaterial increase in valuation allowance on the Company's net deferred tax assets was recorded in various jurisdictions during the second quarter of 2022.

As of December 31, 2022, the Company had the following significant valuation allowances (in thousands):

Jurisdiction	December 31, 2022
Ireland	$ 289,500
Luxembourg	$ 8,862,060
U.S.	$ 1,278,026

The Company maintains a full valuation allowance against the net deferred tax assets in the U.S., Luxembourg, Ireland and certain other foreign tax jurisdictions as of December 31, 2022. It is possible that within the next 12 months there may be sufficient positive evidence to release a portion or all of the valuation allowance. Release of these valuation allowances would result in a benefit to income tax expense for the period the release is recorded, which could have a material impact on net earnings. The timing and amount of the potential valuation allowance release are subject to significant management judgment and prospective earnings.

We have provided for any applicable income taxes associated with current year distributions, as well as any earnings that are expected to be distributed in the future, in the calculation of the income tax provision. As a result of the bankruptcy filing, we have reassessed our historical indefinite reinvestment assertion with respect to undistributed earnings. Based on that reassessment, we have determined that the undistributed earnings of certain subsidiaries will continue to be indefinitely reinvested. Those entities for which we will continue to assert indefinite reinvestment have an accumulated earnings deficit as of December 31, 2022. No additional provision has been made for Irish and non-Irish income taxes on those undistributed earnings that we are not asserting indefinite reinvestment as no tax is expected to be incurred with respect to those earnings. A liability could arise if our intention to indefinitely reinvest such earnings were to change and amounts are distributed by such subsidiaries or if such subsidiaries are ultimately disposed. The potential tax implications of unremitted earnings are driven by the facts at the time of the distribution. It is not practicable to estimate the additional income taxes related to indefinitely reinvested earnings or the basis differences related to investments in subsidiaries.

Uncertain Tax Positions

The Company and its subsidiaries are subject to income taxes in the U.S., various states and numerous foreign jurisdictions with varying statutes as to which tax years are subject to examination by the tax authorities. The Company has taken positions on its tax returns that may be challenged by various tax authorities. The Company believes it has appropriately established reserves for tax-related uncertainties. The Company endeavors to resolve matters with a tax authority at the examination level and could reach agreement with a tax authority at any time. The accruals for tax-related uncertainties are based on the Company's best estimate of the potential tax exposures. When particular matters arise, a number of years may elapse before such matters are audited and finally resolved. The final outcome with a tax authority may result in a tax liability that is more or less than that reflected in our financial statements. Favorable resolution of such matters could be recognized as a reduction of the Company's effective tax rate in the year of resolution, while a resolution that is not favorable could increase the effective tax rate and may require the use of cash. Uncertain tax positions are reviewed quarterly and adjusted as necessary when events occur that affect potential tax liabilities, such as lapsing of applicable statutes of limitations, proposed assessments by tax authorities, identification of new issues and issuance of new legislation, regulations or case law.

As of December 31, 2022, the Company had total UTPs, including accrued interest and penalties, of $646.4 million. If recognized in future years, $251.4 million of such amounts would impact the income tax provision and effective tax rate. As of December 31, 2021, the Company had total UTPs, including accrued interest and penalties, of $620.0 million. If recognized in future years, $241.0 million of such amounts would have impacted the income tax provision and effective tax rate. The following table summarizes the activity related to UTPs during the years ended December 31, 2022, 2021 and 2020 (in thousands):

	Unrecognized Tax Positions Federal, State and Foreign Tax
UTP Balance at December 31, 2019	$ 486,481
Gross additions for current year positions	33,402
Gross reductions for prior period positions	(577)
Gross additions for prior period positions	16,914
Decrease due to lapse of statute of limitations	(7,033)
Currency translation adjustment	588
UTP Balance at December 31, 2020	$ 529,775
Gross additions for current year positions	36,662
Gross reductions for prior period positions	(702)
Gross additions for prior period positions	1,203
Decrease due to lapse of statute of limitations	(475)
Currency translation adjustment	(24)
UTP Balance at December 31, 2021	$ 566,439
Gross additions for current year positions	20,061
Decrease due to lapse of statute of limitations	(4,451)
Currency translation adjustment	(2,419)
UTP Balance at December 31, 2022	$ 579,630
Accrued interest and penalties	66,736
Total UTP balance including accrued interest and penalties	$ 646,366

The Company records accrued interest and penalties, where applicable, related to uncertain tax positions as part of the provision for income taxes. The cumulative accrued interest and penalties related to uncertain tax positions were $66.7 million and $53.6 million as of December 31, 2022 and 2021, respectively.

During the year ended December 31, 2022, the Company recognized net expense of $16.2 million associated with UTPs, primarily related to interest and penalties. During the year ended December 31, 2021, the Company recognized net expense of $10.6 million associated with UTPs, primarily related to interest and penalties. During the year ended December 31, 2020, the Company recognized a net benefit of $78.2 million as a reduction to our net UTP liability, primarily related to the CARES Act. At December 31, 2022, the Company's UTP liability is included in the Consolidated Balance Sheets within Liabilities subject to compromise, Other liabilities and, where appropriate, as a reduction to Deferred tax assets. At December 31, 2021, the Company's UTP liability is included in the Consolidated Balance Sheets within Other liabilities and, where appropriate, as a reduction to Deferred tax assets.

Our subsidiaries file income tax returns in the countries in which they have operations. Generally, these countries have statutes of limitations ranging from 3 to 5 years. Certain subsidiary tax returns are currently under examination by taxing authorities, including U.S. tax returns for the 2006 through 2018 tax years by the IRS.

It is expected that the amount of UTPs will change during the next 12 months; however, we do not currently anticipate any adjustments that would lead to a material impact on our results of operations or our financial position.

On June 3, 2020, in connection with the IRS's examination of our U.S. income tax return for the fiscal year ended December 31, 2015 (2015 Return), we received an acknowledgement of facts (AoF) from the IRS related to transfer pricing positions taken by Endo U.S., Inc. and its subsidiaries (Endo U.S.). The AoF asserted that Endo U.S. overpaid for certain pharmaceutical products that it purchased from certain non-U.S. related parties and proposed a specific adjustment to our 2015 U.S. income tax return position. On September 4, 2020, we received a Form 5701 Notice of Proposed Adjustment (NOPA) that is consistent with the previously disclosed AoF. We believe that the terms of the subject transactions are consistent with comparable transactions for similarly situated unrelated parties, and we intend to contest the proposed adjustment. While the NOPA is not material to our business, financial condition, results of operations or cash flows, the IRS could seek to apply its position to subsequent tax periods and propose similar adjustments. The aggregate impact of these adjustments, if sustained, could have a material adverse effect on our business, financial condition, results of operations and cash flows. Although the timing of the outcome of this matter is uncertain, it is possible any final resolution of the matter could take a number of years.

In connection with the IRS's examination of our 2015 Return, on December 31, 2020, the IRS issued a Technical Advice Memorandum (TAM) regarding the portion of our 2015 NOL that we believe qualifies as a specified product liability loss (SLL). The TAM concurred in part with our positions on the 2015 Return but disagreed with our position that the AMS worthless stock loss qualifies as an SLL. In April 2021, we received draft NOPAs from the IRS consistent with the TAM. We continue to disagree with the IRS's position and the draft NOPAs received and, if necessary, intend to contest any additional tax determined to be owed with respect to the NOPAs. However, if we were unsuccessful in contesting the IRS's position, we have preliminarily estimated that we would have additional cash taxes payable to the IRS of between $70 million and $250 million excluding interest. We continue to discuss this position with the IRS and the actual amount that may be owed to the IRS if we are unsuccessful may be different than our preliminary estimate. Although the timing of the outcome of this matter is uncertain, it is possible any final resolution of the matter could take a number of years.

As of December 31, 2022, we may be subject to examination in the following major tax jurisdictions:

Jurisdiction	Open Years
Canada	2016 through 2022
India	2012 through 2022
Ireland	2016 through 2022
Luxembourg	2015 through 2022
U.S. - federal, state and local	2006 through 2022

Bankruptcy-Related Developments

In connection with our ongoing bankruptcy proceedings, the IRS has filed multiple proofs of claim against several of the Debtors. The total amount of the claims filed by the IRS, which relate to tax years ended 2006 through 2014, 2016 through 2018 and 2020 through 2021, is approximately $18.7 billion. A number of the claims are in respect of the same proposed tax liability but are filed against multiple subsidiary members of our U.S. consolidated tax groups. After excluding the repetitive claims filed to different members of our U.S. consolidated tax groups, the net claims are approximately $2.6 billion. We did not receive from the IRS calculations or support for the amount of the claims filed; however, through our discussions with the IRS following the submission of the claims, we understand that the claims primarily relate to the IRS's challenges of our historic tax positions discussed above for certain intercompany arrangements, including the level of profit earned by our U.S. subsidiaries pursuant to such arrangements, and a product liability loss carryback claim. We disagree with the IRS's claims and, if necessary, intend to contest any additional tax determined to be owed with respect to the claims.

NOTE 22. NET (LOSS) INCOME PER SHARE

The following is a reconciliation of the numerator and denominator of basic and diluted net (loss) income per share for the years ended December 31, 2022, 2021 and 2020 (in thousands):

	2022	2021	2020
Numerator:			
(Loss) income from continuing operations	$ (2,909,618)	$ (569,081)	$ 247,464
Income (loss) from discontinued operations, net of tax	(13,487)	(44,164)	(63,520)
Net (loss) income	$ (2,923,105)	$ (613,245)	$ 183,944
Denominator:			
For basic per share data—weighted average shares	234,840	232,785	229,314
Dilutive effect of ordinary share equivalents	—	—	4,339
For diluted per share data—weighted average shares	234,840	232,785	233,653

Basic per share amounts are computed based on the weighted average number of ordinary shares outstanding during the period. Diluted per share amounts are computed based on the weighted average number of ordinary shares outstanding and, if there is net income from continuing operations during the period, the dilutive effect of ordinary share equivalents outstanding during the period.

The dilutive effect of ordinary share equivalents is measured using the treasury stock method. Any stock options and/or awards that have been issued but for which a grant date has not yet been established are not considered in the calculation of basic or diluted weighted average shares.

The following table presents, for the years ended December 31, 2022, 2021 and 2020, outstanding stock options and stock awards that could potentially dilute per share amounts in the future that were not included in the computation of diluted per share amounts for the periods presented because to do so would have been antidilutive (in thousands):

	2022	2021	2020
Stock options	5,453	6,584	7,073
Stock awards	5,789	9,256	5,197

NOTE 23. CONDENSED COMBINED DEBTOR-IN-POSSESSION FINANCIAL INFORMATION

The financial statements included in this Note represent the Condensed Combined Financial Statements of the Debtors only, which include Endo International plc and most of its wholly-owned subsidiaries, except for its Indian subsidiaries and certain subsidiaries associated with the Company's former Astora business. These statements reflect the results of operations, financial position and cash flows of the combined Debtors, including certain amounts and activities between Debtors and Non-Debtor Affiliates of the Company that are eliminated in the Consolidated Financial Statements.

CONDENSED COMBINED BALANCE SHEETS
(Dollars in thousands)

	December 31, 2022
ASSETS	
CURRENT ASSETS:	
Cash and cash equivalents	$ 991,901
Restricted cash and cash equivalents	59,358
Accounts receivable, net	478,889
Inventories, net	241,349
Prepaid expenses and other current assets	111,807
Income taxes receivable	7,038
Receivables from Non-Debtor Affiliates	94,608
Total current assets	$ 1,984,950
PROPERTY, PLANT AND EQUIPMENT, NET	233,114
OPERATING LEASE ASSETS	23,200
GOODWILL	1,352,011
OTHER INTANGIBLES, NET	1,732,935
INVESTMENTS IN NON-DEBTOR AFFILIATES	50,001
RECEIVABLES FROM NON-DEBTOR AFFILIATES	240,002
OTHER ASSETS	126,494
TOTAL ASSETS	$ 5,742,707
LIABILITIES AND DEFICIT	
CURRENT LIABILITIES:	
Accounts payable and accrued expenses	$ 654,414
Current portion of operating lease liabilities	230
Income taxes payable	10
Payables to Non-Debtor Affiliates	20,162
Total current liabilities	$ 674,816
DEFERRED INCOME TAXES	13,479
OPERATING LEASE LIABILITIES, LESS CURRENT PORTION	994
OTHER LIABILITIES	37,367
LIABILITIES SUBJECT TO COMPROMISE	9,168,782
TOTAL DEFICIT	(4,152,731)
TOTAL LIABILITIES AND DEFICIT	$ 5,742,707

CONDENSED COMBINED STATEMENTS OF OPERATIONS
(Dollars in thousands)

	2022
TOTAL REVENUES, NET	$ 2,321,426
COSTS AND EXPENSES:	
Cost of revenues	1,106,855
Selling, general and administrative	764,768
Research and development	137,851
Acquired in-process research and development	68,700
Litigation-related and other contingencies, net	478,722
Asset impairment charges	2,137,107
Acquisition-related and integration items, net	408
Interest expense, net	345,593
Reorganization items, net	202,978
Other income, net	(13,409)
LOSS FROM CONTINUING OPERATIONS BEFORE INCOME TAX	$ (2,908,147)
INCOME TAX EXPENSE	17,721
LOSS FROM CONTINUING OPERATIONS	$ (2,925,868)
DISCONTINUED OPERATIONS, NET OF TAX	(13,468)
NET LOSS ATTRIBUTABLE TO DEBTOR ENTITIES	$ (2,939,336)
EQUITY IN INCOME OF NON-DEBTOR AFFILIATES, NET OF TAX	22,671
NET LOSS	$ (2,916,665)

CONDENSED COMBINED STATEMENTS OF COMPREHENSIVE LOSS
(Dollars in thousands)

	2022
NET LOSS	$ (2,916,665)
OTHER COMPREHENSIVE LOSS:	
Net unrealized loss on foreign currency	$ (10,496)
Total other comprehensive loss	$ (10,496)
COMPREHENSIVE LOSS	$ (2,927,161)

CONDENSED COMBINED STATEMENTS OF CASH FLOWS
(Dollars in thousands)

	2022
OPERATING ACTIVITIES:	
Net cash provided by operating activities (1)	$ 209,523
INVESTING ACTIVITIES:	
Capital expenditures, excluding capitalized interest	(43,743)
Capitalized interest payments	(3,140)
Proceeds from the U S Government Agreement	18,635
Acquisitions, including in-process research and development, net of cash and restricted cash acquired	(90,320)
Proceeds from sale of business and other assets, net	41,400
Proceeds from loans made to Non-Debtor Affiliates	2,355
Disbursements for loans made to Non-Debtor Affiliates	(51,486)
Net cash used in investing activities	$ (126,299)
FINANCING ACTIVITIES:	
Repayments of notes	(180,342)
Repayments of term loans	(10,000)
Adequate protection payments	(313,109)
Repayments of other indebtedness	(6,062)
Payments for contingent consideration	(2,462)
Payments of tax withholding for restricted shares	(1,898)
Net cash used in financing activities	$ (513,873)
Effect of foreign exchange rate	(1,790)
NET DECREASE IN CASH, CASH EQUIVALENTS, RESTRICTED CASH AND RESTRICTED CASH EQUIVALENTS	$ (432,439)
CASH, CASH EQUIVALENTS, RESTRICTED CASH AND RESTRICTED CASH EQUIVALENTS, BEGINNING OF PERIOD	1,568,698
CASH, CASH EQUIVALENTS, RESTRICTED CASH AND RESTRICTED CASH EQUIVALENTS, END OF PERIOD	$ 1,136,259

(1) The difference between the amount of Net cash provided by operating activities included in the table above and the amount of Net cash provided by operating activities included in the Consolidated Statements of Cash Flows for the same period primarily relates to the fact that the table above: (i) excludes the operating cash flows of our Non-Debtor Affiliates, which are included in the Consolidated Statements of Cash Flows, and (ii) includes the effects of the operating cash flows of the Debtors with the Non-Debtor Affiliates, which are eliminated in the Consolidated Statements of Cash Flows

NOTE 24. SAVINGS AND INVESTMENT PLAN AND DEFERRED COMPENSATION PLANS

Savings and Investment Plan

The Company maintains a defined contribution Savings and Investment Plan (the Endo 401(k) Plan) covering all U.S.-based eligible employees. The Company matches 100% of the first 3% of eligible cash compensation that a participant contributes to the Endo 401(k) Plan plus 50% of the next 2% for a total of up to 4%, subject to statutory limitations. The Company's matching contributions generally vest ratably over a two-year period.

Costs incurred for contributions made by the Company to the Endo 401(k) Plan amounted to $6.5 million, $7.6 million and $7.6 million for the years ended December 31, 2022, 2021 and 2020, respectively.

Exhibit 21.1

SUBSIDIARIES OF THE REGISTRANT

The following is a list of the subsidiaries of the Company as of December 31, 2022.

Subsidiary	Jurisdiction of Incorporation or Organization	Ownership by Endo International plc
70 Maple Avenue, LLC	Delaware	Indirect
Actient Pharmaceuticals LLC	Delaware	Indirect
Actient Therapeutics, LLC	Delaware	Indirect
Anchen Incorporated	New York	Indirect
Anchen Pharmaceuticals, Inc	Delaware	Indirect
Astora Women's Health Bermuda ULC	Bermuda	Indirect
Astora Women's Health Ireland Limited	Ireland	Indirect
Astora Women's Health Technologies	Ireland	Indirect
Astora Women's Health, LLC	Delaware	Indirect
Auxilium International Holdings, LLC	Delaware	Indirect
Auxilium Pharmaceuticals, LLC	Delaware	Indirect
Auxilium US Holdings, LLC	Delaware	Indirect
BioSpecifics Technologies LLC	Delaware	Indirect
Bermuda Acquisition Management Limited	Bermuda	Indirect
Branded Operations Holdings, Inc	Delaware	Indirect
CPEC LLC	Delaware	Indirect
DAVA International, LLC	Delaware	Indirect
DAVA Pharmaceuticals, LLC	Delaware	Indirect
Endo Aesthetics LLC	Delaware	Indirect
Endo Bermuda Finance Limited	Bermuda	Indirect
Endo Designated Activity Company	Ireland	Direct
Endo Eurofin Unlimited Company	Ireland	Indirect
Endo Finance IV Unlimited Company	Ireland	Indirect
Endo Finance LLC	Delaware	Indirect
Endo Finance Operations LLC	Delaware	Indirect
Endo Finco Inc	Delaware	Indirect
Endo Generics Holdings, Inc	Delaware	Indirect
Endo Global Aesthetics Limited	Ireland	Indirect
Endo Global Biologics Limited	Ireland	Indirect
Endo Global Development Limited	Ireland	Indirect
Endo Global Finance LLC	Delaware	Indirect
Endo Global Ventures	Bermuda	Indirect
Endo Health Solutions Inc	Delaware	Indirect
Endo Innovation Valera, LLC	New York	Indirect
Endo Ireland Finance II Limited	Ireland	Indirect
Endo LLC	Delaware	Indirect
Endo Luxembourg Finance Company I S a r l	Luxembourg	Indirect
Endo Luxembourg Holding Company S a r l	Luxembourg	Indirect
Endo Luxembourg International Financing S a r l	Luxembourg	Indirect
Endo Management Limited	Ireland	Indirect
Endo Par Innovation Company, LLC	Delaware	Indirect
Endo Pharmaceuticals Finance LLC	Delaware	Indirect
Endo Pharmaceuticals Inc	Delaware	Indirect
Endo Pharmaceuticals Solutions Inc	Delaware	Indirect
Endo Pharmaceuticals Valera Inc	Delaware	Indirect
Endo Procurement Operations Limited	Ireland	Indirect
Endo TopFin Limited	Ireland	Indirect
Endo U S Inc	Delaware	Indirect
Endo US Holdings Luxembourg I S a r l	Luxembourg	Indirect
Endo Ventures Aesthetics Limited	Ireland	Indirect
Endo Ventures Bermuda Limited	Bermuda	Indirect
Endo Ventures Cyprus Limited	Cyprus	Indirect

Subsidiary	Jurisdiction of Incorporation or Organization	Ownership by Endo International plc
Endo Ventures Limited	Ireland	Indirect
Generics Bidco I, LLC	Delaware	Indirect
Generics International (US) 2, Inc	Delaware	Indirect
Generics International (US), Inc	New York	Indirect
Generics International Ventures Enterprises LLC	Pennsylvania	Indirect
Hawk Acquisition Ireland Limited	Ireland	Indirect
Innoteq, Inc	Delaware	Indirect
JHP Acquisition, LLC	Delaware	Indirect
JHP Group Holdings, LLC	Delaware	Indirect
Kali Laboratories 2, Inc	Delaware	Indirect
Kali Laboratories, LLC	New Jersey	Indirect
Luxembourg Endo Specialty Pharmaceuticals Holding I S a r l	Luxembourg	Indirect
Moores Mill Properties L L C	Delaware	Indirect
Paladin Labs Canadian Holding Inc	Canada	Indirect
Paladin Labs Inc	Canada	Indirect
Par Active Technologies Private Limited	India	Indirect
Par Biosciences Private Limited	India	Indirect
Par Formulations Private Limited	India	Indirect
Par Laboratories Europe, Ltd	England and Wales	Indirect
Par Pharmaceutical 2, Inc	Delaware	Indirect
Par Pharmaceutical Companies, Inc	Delaware	Indirect
Par Pharmaceutical Holdings, Inc	Delaware	Indirect
Par Pharmaceutical, Inc	New York	Indirect
Par Sterile Products, LLC	Delaware	Indirect
Par, LLC	Delaware	Indirect
Quartz Specialty Pharmaceuticals, LLC	Delaware	Indirect
Slate Pharmaceuticals, LLC	Delaware	Indirect
Timm Medical Holdings, LLC	Delaware	Indirect
Vintage Pharmaceuticals, LLC	Delaware	Indirect

POWER OF ATTORNEY

Each of the undersigned, hereby constitutes and appoints each of Blaise Coleman, Mark T. Bradley, Matthew J. Maletta and Brian Morrissey to be his or her true and lawful attorneys-in-fact and agents, with full power of each to act alone, and to sign for the undersigned and in each of their respective names in any and all capacities stated below, this Annual Report on Form 10-K (and any amendments hereto) and to file the same, with exhibits hereto and thereto and other documents in connection herewith and therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact, or his or her substitute or substitutes, may do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this Power of Attorney has been signed by the following persons in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Mark G. Barberio Mark G. Barberio	Chairman and Director	March 3, 2023
/s/ Jennifer M. Chao Jennifer M. Chao	Director	March 3, 2023
/s/ Shane M. Cooke Shane M. Cooke	Director	March 3, 2023
/s/ Nancy J. Hutson, Ph.D. Nancy J. Hutson, Ph.D.	Director	March 3, 2023
/s/ Michael Hyatt Michael Hyatt	Director	March 3, 2023
/s/ William P. Montague William P. Montague	Director	March 3, 2023
/s/ M. Christine Smith, Ph.D. M. Christine Smith, Ph.D.	Director	March 3, 2023

CERTIFICATION OF CHIEF EXECUTIVE OFFICER
PURSUANT TO SECTION 302 OF
THE SARBANES-OXLEY ACT OF 2002

I, Blaise Coleman, certify that:

1. I have reviewed this annual report on Form 10-K of Endo International plc;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's Board of Directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

/S/ BLAISE COLEMAN

Blaise Coleman
President and Chief Executive Officer
(Principal Executive Officer)

Date: March 6, 2023

CERTIFICATION OF CHIEF FINANCIAL OFFICER
PURSUANT TO SECTION 302 OF
THE SARBANES-OXLEY ACT OF 2002

I, Mark T. Bradley, certify that:

1. I have reviewed this annual report on Form 10-K of Endo International plc;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's Board of Directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

/S/ MARK T. BRADLEY

Mark T. Bradley
Executive Vice President, Chief Financial Officer
(Principal Financial Officer)

Date: March 6, 2023

CERTIFICATION OF CHIEF EXECUTIVE OFFICER
PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

I, Blaise Coleman, as President and Chief Executive Officer of Endo International plc (the Company), hereby certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Annual Report on Form 10-K of the Company for the annual period ended December 31, 2022 (the Report) fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934 (15 U.S.C. 78m); and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/S/ BLAISE COLEMAN

Name: Blaise Coleman
Title: President and Chief Executive Officer
(Principal Executive Officer)

Date: March 6, 2023

A signed original of this written statement required by Section 906 has been provided to, and will be retained by, Endo International plc and furnished to the Securities and Exchange Commission or its staff upon request.

CERTIFICATION OF CHIEF FINANCIAL OFFICER
PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

I, Mark T. Bradley, as Chief Financial Officer of Endo International plc (the Company), hereby certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Annual Report on Form 10-K of the Company for the annual period ended December 31, 2022 (the Report) fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934 (15 U.S.C. 78m); and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/S/ MARK T. BRADLEY

Name: Mark T. Bradley

Title: Executive Vice President, Chief Financial Officer
(Principal Financial Officer)

Date: March 6, 2023

A signed original of this written statement required by Section 906 has been provided to, and will be retained by, Endo International plc and furnished to the Securities and Exchange Commission or its staff upon request.

This is **Exhibit "2"** referred to in the Affidavit sworn remotely by Nick Boorman, stated as being at the City of Toronto, in the Province of Ontario, before me at the City of Toronto, in the Province of Ontario, on September 29, 2023, in accordance with O. Reg. 431/20, *Administering Oath or Declaration Remotely*

A Commissioner, etc.

Exhibit "3"

Notice of clarification to drug manufacturers and sponsors - Risk Management Plans - Update

August 13, 2020

Purpose

This notice is being issued to clarify to drug manufacturers and sponsors that elements of Risk Management Plans (RMPs) required by Health Canada, such as controlled distribution programs, are not intended to restrict access to Canadian Reference Products (CRPs) for generic drug manufacturers for the purposes of conducting comparative testing. Any RMP elements should not delay or hinder comparative testing with generic products or hinder their ability to enter the market.

Implementation of RMPs in Canada

In February 2009, Health Canada announced the implementation of risk management planning and in June 2015 released the Guidance Document *Submission of Risk Management Plans and Follow-up Commitments*.

Quick Facts on RMPs

An RMP is a document that outlines pharmacovigilance activities and interventions to identify, characterize, prevent or minimize risks related to drug products. The RMP also contains an evaluation of the effectiveness of such risk minimization measures.

Risk minimization measures in an RMP aim to optimize the safe and effective use of a drug throughout its life cycle (e.g. appropriate labelling). However, for certain drugs with serious risks, more restrictive measures may be required when labelling alone is not enough to ensure the benefits outweigh the risks. For these drugs, Health Canada may require more restrictive risk minimization measures, such as a controlled distribution program. Under such programs, drugs may only be distributed through certain channels, and pharmacies, physicians, and patients may need to register to access the drug.

RMPs and Access to CRPs for Generic Drug Manufacturers

Before a generic drug can enter the market, a generic drug manufacturer must prove that the drug is safe and effective by submitting comparative testing to demonstrate that it is pharmaceutically equivalent to the branded drug. To complete this testing, the manufacturer needs access to samples of the branded drug, also known as the CRP. These studies are then submitted to Health Canada for regulatory approval to market the generic drug.

Manufacturers of branded drugs cannot use elements of an RMP, such as a controlled distribution program, to prevent generic drug manufacturers from conducting comparative testing. A branded manufacturer that

provides samples of the branded drug to a generic manufacturer to conduct comparative testing is not violating the RMP.

Moreover, comparative testing by a generic manufacturer falls under the clinical trial regulatory framework. This framework contains ways to protect the safety of clinical trial participants. See Part C, Division 5 of the Guidance Document - *Drugs for Clinical Trials Involving Human Subjects*.

Health Canada is committed to making sure that RMPs continue to contribute to patient safety. It also reminds sponsors that RMP elements should not be seen as a reason to delay or stop comparative testing with generic products, or to prevent them from entering the market.

For inquiries related to this communication, contact Health Canada at:

Marketed Health Products Directorate (MHPD)
E-mail: mhpd-dpsc@canada.ca
Telephone: 613-954-6522
Fax: 613-952-7738

Date modified:
2020-08-13

This is **Exhibit "3"** referred to in the Affidavit sworn remotely by Nick Boorman, stated as being at the City of Toronto, in the Province of Ontario, before me at the City of Toronto, in the Province of Ontario, on September 29, 2023, in accordance with O. Reg. 431/20, *Administering Oath or Declaration Remotely*

A Commissioner, etc.

Exhibit "4"

Investigation into alleged practices of Celgene, Pfizer and Sanofi

Position Statement

See the news release that corresponds to this position statement.

OTTAWA, December 20, 2018 — Today, the Interim Commissioner of Competition announced that he has discontinued his inquiry relating to policies or practices of certain branded drug manufacturers, which were alleged to restrict generic drug manufacturers' access to samples of their branded products contrary to the abuse of dominance provisions of the *Competition Act* (**Act**).

This position statement summarizes the analysis and conclusions of the Competition Bureau's investigation and the reasons for discontinuing the Inquiry. While the Bureau has not concluded that the Act has been contravened at this time, the practices within the pharmaceutical industry that gave rise to its investigation are of concern to the Bureau, and may warrant further enforcement or advocacy action in the future.

I. Background: The Pharmaceutical Industry

Pharmaceuticals comprised 16.4% of total health care expenditures in Canada in 2017. [1] On average, annual pharmaceutical expenditure per capita was approximately $1,086. [2] Because of the important role of pharmaceuticals in treating illnesses and improving the lives of patients, vigorous competition among pharmaceutical manufacturers is essential in order to ensure that Canadian consumers benefit from low drug prices and continued innovation.

Canada's regulatory and intellectual property framework is aimed at balancing incentives for branded pharmaceutical manufacturers (**Brands**) to provide Canadians access to new and innovative drugs on one hand, and the benefits that come from access to lower priced drugs from generic drug manufacturers (**Generics**) on the other.

Brands incur significant costs in researching and commercializing branded pharmaceuticals, including costs to comply with regulatory requirements. Before marketing a branded pharmaceutical, Brands need to obtain the approval of the Minister of Health. Among other things, seeking approval of a new drug involves conducting extensive clinical trials to prove that the new drug is safe and effective. Brands typically apply for patent and other protections that enable them to enjoy some degree of time-limited market exclusivity, providing a period of time where they can introduce a branded pharmaceutical and be insulated from competition. This serves as an incentive for Brands to continue making investments and developing innovative therapies.

Following the expiry, successful challenge or negotiated agreement related to a Brand's intellectual property, competition from generic drugs typically emerges. Generic drugs are therapeutically equivalent to branded drugs, and are usually sold at a significantly lower price. Typically, the first generic drug introduced to the market, whether following patent expiry, negotiated agreement or a successful patent validity challenge, is priced at 85% (or less) of the cost of the branded pharmaceutical. Subsequent generic drugs further decrease the drug price. For example, the introduction of the third generic drug typically decreases the drug price to 25% of the branded pharmaceutical. [3]

One of the reasons why generic drugs are less expensive than branded drugs is that Generics generally rely on the clinical testing that the Brand had conducted to prove the drug was safe and effective, resulting in significant

cost savings. However, in order to do so, a Generic must prove that its product is “bio-equivalent” – that is, prove it is therapeutically equivalent – to the branded drug, which generally requires samples of the branded drug (**Canadian Reference Products** or **CRPs**). Without access to CRPs a Generic cannot conduct bioequivalence testing, and therefore in many cases cannot receive the necessary regulatory approval to market the generic drug. As a result, if a Brand can prevent or delay Generics from accessing CRPs, this may limit competition from Generics and deny Canadians timely access to safe and effective generic drugs at lower prices.

II. The Inquiry

In 2016, the Bureau was made aware of certain alleged conduct by Brands that may foreclose or delay the ability of Generics to obtain sufficient amounts of CRPs to secure regulatory approvals, thereby delaying the marketing of generic equivalents. [4] In particular, Generics alleged that they have been increasingly impeded in access to CRPs through pharmaceutical wholesalers, [5] who typically serve as intermediaries in the supply chain between pharmaceutical manufacturers and downstream purchasers such as pharmacies and hospitals. Based on preliminary information from relevant market participants, the Commissioner initiated an inquiry in November 2016. Specifically, the Bureau inquired into the conduct of certain Brands, including Celgene, Inc., Pfizer Canada, Inc. and Sanofi-Aventis Canada, Inc.

The Inquiry focused on two types of conduct. First, the Bureau looked into alleged restrictions imposed by Celgene, Pfizer and Sanofi on wholesalers or other distributors that may prevent them from supplying CRPs to Generics. Second, the Bureau examined the approach taken by Brands in dealing with requests for CRPs they receive directly from Generics.

The Bureau assessed the allegations under the abuse of dominance provisions of the Act. Under the Act, abuse of dominance occurs when a dominant firm or group of firms in a market, engages in a practice of anti-competitive acts, with the result that competition has been or is likely to be lessened or prevented substantially.

Over the course of its investigation, the Bureau gathered information from numerous third-parties, including key private and public stakeholders in the pharmaceutical industry, as well as information directly from Celgene, Pfizer and Sanofi pursuant to a court order.

The conduct examined by the Bureau during the course of the Inquiry varied to a degree by Brand and the findings are therefore explained below in groupings.

A. Bureau Findings – Celgene

The Bureau's investigation into Celgene's practices focussed on two issues:

i. whether Celgene's risk management program was anti-competitive due to explicit distribution restrictions that prevented Generics from accessing CRPs from pharmaceutical wholesalers; and
ii. whether Celgene's approach in dealing with direct requests for CRPs from Generics materially delayed or blocked the marketing of the Generic version of the drug.

i. Celgene's risk management program

In order to market certain pharmaceuticals, Health Canada requires the implementation of a risk management program to mitigate the health and safety risks associated with uncontrolled distribution and dispensing of high risk drugs. Revlimid, one of Celgene's products, is used to treat various cancers, such as multiple myeloma, but also poses significant risks to fetal

development, causing life-threatening deformities and abnormalities when exposed to patients during pregnancy. Revlimid is subject to a risk management program, known as RevAid.

Among other things, the RevAid program includes distribution of Revlimid through limited channels, and registration of pharmacies, physicians, and patients who may access Revlimid. Through this system, Celgene is able to limit the distribution of Revlimid to specific entities or individuals that will be provided access to these pharmaceuticals. These restrictions on distribution raised concerns that elements of the RevAid program may go beyond what was necessary to address health and safety concerns posed by Revlimid in order to limit the ability of Generics to access CRPs.

Based on the information the Bureau has gathered, there is insufficient evidence to conclude that the elements of the RevAid program that limit distribution to Generics are anti-competitive. That is, at this time the Bureau has not concluded they go beyond legitimate measures to ensure safe use of Revlimid or other regulatory requirements.

ii. Celgene's approach to direct requests for CRPs from Generics

One consequence of the RevAid program is that Generics may be forced to approach Celgene directly in order to obtain CRPs for drugs subject to the program. Thus, even if the RevAid program is not itself anti-competitive, it may contribute to other potentially anti-competitive conduct relating to Celgene's treatment of requests by Generics to purchase CRPs.

Based on the information gathered in the course of the Inquiry, the Bureau found that Generics have indeed requested CRPs directly from Celgene on more than one occasion. However, the Bureau is not aware of any instance where a request for restricted CRPs has been fulfilled by Celgene due to

various reasons. In at least one case, Celgene has imposed conditions on the supply to a Generic, which the Generic has characterized as unnecessary and burdensome.

While these requests remained unfulfilled by Celgene, the Bureau was made aware of the fact that certain Generics were ultimately able to obtain sufficient CRPs through other means. The Bureau's decision to discontinue its investigation against Celgene turned on this fact as well as on the fact that these Generics were eventually able to conduct the necessary studies to make the submissions needed for Health Canada approval.

Consequently, in spite of finding some evidence suggesting that Celgene's conduct resulted in some delays, difficulties and costs to Generics, at this time there is insufficient evidence to conclude that Celgene's conduct gives rise to a substantial lessening or prevention of competition – one of three elements needed to demonstrate that Celgene is contravening the abuse of dominance provisions of the Act.

B. Bureau Findings – Pfizer and Sanofi

In addition to Celgene, the Bureau also inquired into allegations against certain other Brands, including Pfizer and Sanofi, had restricted the supply of CRPs to Generics by wholesalers. The Bureau did not find sufficient evidence suggesting that these parties have policies or practices that have the effect of inhibiting Generics from obtaining CRPs and substantially delaying or preventing their entry. Notably, over the course of the investigation, the Bureau has also become aware that one or more Generics have generally obtained the CRPs that were the specific focus of the Inquiry.

In particular, the Bureau commends Pfizer for its cooperation during the Inquiry. In June 2018, Pfizer sent a notice letter to relevant internal staff and distributors confirming that it does not have a policy restricting Generics' access to its pharmaceutical products, and that there should be no

discrimination between Generics and other customers. While the Bureau concluded that Pfizer has not violated the Act or engaged in any wrongdoing, the Bureau wishes to acknowledge Pfizer's proactive measures to ensure clarity of its policies.

III. Guidance to the Pharmaceutical Industry

The Bureau's investigation into the practices by certain Brands raised many important competition issues that are of relevance to various participants in the pharmaceutical industry. Some of these issues are highlighted below and are intended to provide guidance to market participants:

A. Assessing market power in the pharmaceutical industry

When assessing allegations of abuse of dominance, the Bureau will generally define one or more relevant markets, consisting of both a product and geographic dimension. With respect to the product dimension, although the Bureau has not reached any final conclusions, in this particular case the Bureau has generally proceeded on the basis that drugs containing a particular active ingredient constitute a relevant market (i.e., in most cases, the market is the branded drug and its generics). Due to the fact pharmaceuticals are generally marketed on a national basis, the starting point of the Bureau's analysis would be to consider that the relevant geographic market is national.

Given such market definition, prior to Generic entry the Bureau would generally consider that a Brand would have sufficient market power to satisfy the first element of the abuse of dominance provisions. Among other things, prior to Generic entry a brand would typically hold a 100% market share and would be insulated from competition by barriers such as intellectual property protections.

B. Inhibiting a potential competitor's ability to prepare for market entry

In the course of the Inquiry, the Bureau considered whether the conduct at issue is subject to the exception contained in subsection 79(5) [6] of the Act. The Bureau is of the view that the conduct at issue goes beyond the mere exercise of an intellectual property right and may engage the abuse of dominance provisions.

In this particular case, the evidence gathered supports the position that Generics may at times face barriers that impede their access to CRPs, barriers that in some cases are due to actions by Brands. For example, the Bureau's Inquiry has revealed several cases where Generics have had to seek alternate sources of supply to the means through which they typically obtain CRPs, which has introduced delays in obtaining samples as well as increased cost. In such cases, Generics may have been hindered to some degree. However, based on the information gathered at this time, the Bureau has not identified any case where the impact on the ultimate marketing of a generic drug rises to a *substantial* lessening or prevention of competition, the threshold necessary to engage the abuse of dominance provisions.

C. Limited distribution of pharmaceuticals

Over the course of the Inquiry, the Bureau has heard that there is an increasing trend to limited distribution of Brand drugs, for example, in cases where drugs are only distributed from manufacturers to end-users through certain specialty pharmacies. Where such mechanisms are used by Brands to inhibit their potential competitors' ability to penetrate the market, this may raise concerns of potential anti-competitive conduct.

IV. Developments in the United States and the potential for Canadian Policy Action

The allegations examined by the Bureau during the course of this Inquiry are not unique to Canada. On May 31, 2018, the Food and Drug Administration (**FDA**) issued a public statement highlighting the exploitation of risk evaluation and mitigation strategies (**REMS**) in the United States. Similar to Canada, the goal of a REMS program is to improve drug safety in situations where there are significant safety concerns due to high toxicity or other risks. The FDA asserted that Brands have abused FDA-approved REMS programs by:

i. denying Generics access to reference products and
ii. preventing Generics from participating in the Brands' REMS programs even when Generics are in a position to market their Generic Equivalents.

The Bureau is aware that legislative action is underway in the United States in order to address such issues.

In Canada, similar legislative or policy approaches have not yet been undertaken to address the broader issue of access to CRPs for pharmaceuticals that are subject to risk management programs. Although the specific facts of this Inquiry did not permit the Bureau to conclude an abuse of dominance has occurred, there are broader issues in this arena that may benefit from further exploration of policy options.

V. Conclusion

The Bureau remains very mindful of the importance of competition in the pharmaceutical industry especially where potential competitors experience undue difficulties or delays in penetrating the market. In this case, the Commissioner has decided to discontinue his Inquiry as the evidence uncovered by the Bureau to date is insufficient for the Commissioner to

commence legal proceedings before the Competition Tribunal. However, the Bureau is of the view that the type of conduct at issue in the Inquiry has the potential to raise serious concerns under the abuse of dominance provisions.

Should new and compelling evidence of harm come to light, the Bureau will not hesitate to take appropriate action.

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Media Relations
Email: media-cb-bc@cb-bc.gc.ca

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Enquiries/Complaints

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The Competition Bureau, as an independent law enforcement agency, ensures that Canadian businesses and consumers prosper in a competitive and innovative marketplace.

Footnotes

1 See Canadian Institute for Health Information (CIHI), National Health Expenditure Trends, 1975 to 2017.

2 Ibid.

3 See the Tiered Pricing Framework in Table 2 of the Generic and Biosimilar Pricing Policies for Canadian Public Drug Plans compiled by the Patented Medicine Prices Review Board.

4 Section 55.2(1) of the *Patent Act* establishes an “early working” exemption, which provides that use of a patented invention for the purpose of seeking regulatory approvals is not patent infringement.

5 While pharmaceutical wholesalers were relevant to the Inquiry because of the role they play in the supply chain, they were not the target of the Inquiry.

6 Subsection 79(5) states that "For the purpose of this section, an act engaged in pursuant only to the exercise of any right or enjoyment of any interest derived under the *Copyright Act*, *Industrial Design Act*, *Integrated Circuit Topography Act*, *Patent Act*, *Trade-marks Act* or any other Act of Parliament pertaining to intellectual or industrial property is not an anti-competitive act." For information on the Bureau's approach to reviewing business conduct involving intellectual property, see the *Intellectual Property Enforcement Guidelines* (Ottawa: Innovation, Science and Economic Development Canada, 2016).

Date modified:
2022-01-20

ontact the Competition Bureau

This is **Exhibit "4"** referred to in the Affidavit sworn remotely by Nick Boorman, stated as being at the City of Toronto, in the Province of Ontario, before me at the City of Toronto, in the Province of Ontario, on September 29, 2023, in accordance with O. Reg. 431/20, *Administering Oath or Declaration Remotely*

A Commissioner, etc.

Exhibit "5"

Competition Bureau statement regarding its inquiry into alleged anti-competitive conduct by Otsuka

GATINEAU, April 2, 2020—Today, the Commissioner of Competition announced that he has discontinued an inquiry after two months of active investigation into the conduct of Otsuka Canada Pharmaceutical Inc. ("**Otsuka**") after Otsuka took action to address the Commissioner's concerns. Specifically, the Competition Bureau's inquiry considered allegations that Otsuka restricted a generic drug manufacturer ("**Generic**") from accessing samples of its branded product, Jinarc (active ingredient "tolvaptan"), preventing or delaying the entry of competing generic drugs contrary to the abuse of dominance provisions of the *Competition Act* (the "**Act**"). This is the second time the Commissioner has found it appropriate to inquire into refusals to supply samples by branded pharmaceutical companies.

The Bureau previously considered refusals of brand samples to Generics as outlined in a position statement published in December 2018 [1], regarding the Bureau's investigation into alleged practices of other brand pharmaceutical manufacturers ("**2018 Position Statement**"). In the matter described in the 2018 Position Statement, the Bureau investigated policies and practices alleged to restrict Generics from accessing samples of brand name drugs, which are also known as Canadian Reference Products ("**CRPs**"). The Bureau cautioned that the alleged conduct could raise serious issues under the abuse of dominance provisions of the Act and that it would not hesitate to take immediate action in similar circumstances.

As discussed further in the 2018 Position Statement, without access to brand samples, a Generic cannot conduct bioequivalence testing, and therefore in many cases cannot receive the necessary regulatory approval to market the

generic drug. As a result, if a branded drug manufacturer can prevent or delay Generics from accessing these samples, it can limit competition from Generics.

Generics generally rely on the clinical testing that the Brand had conducted to prove the drug was safe and effective, resulting in significant cost savings. This allows Generics to compete with Brand drugs with lower prices. In an effort to balance the incentives of Brand drugs to innovate with the benefits of Generic competition, the Bureau is committed to taking appropriate action to prevent practices by Brand drugs that aim to prevent Generics from competing in the market.

The Bureau re-emphasizes its serious concerns with this conduct and its commitment to addressing these concerns. This matter was ultimately resolved shortly after the Bureau became involved (but approximately one year after the Generic first requested samples). Following Otsuka's supply of Jinarc to the Generic subsequent to the Bureau's intervention and upon being satisfied that the supply had been delivered, the Bureau discontinued its inquiry. Despite this outcome, the Bureau remains very concerned with the course of conduct that is being repeated in the industry.

The Bureau will continue to monitor the pharmaceutical industry for any conduct that prevents or delays the supply of samples of branded drugs to Generics. As this is now the second time the Bureau has provided guidance to the industry on this issue, branded drug manufacturers should be aware that in future even if samples are eventually supplied, the Bureau will take the necessary steps to address past conduct, including seeking administrative monetary penalties, where the evidence establishes the Act is engaged. Given this guidance from the Bureau and the guidance discussed below from Health Canada, branded drug manufacturers should anticipate that the Bureau will treat any explanation for a failure to supply Generics in a timely manner with an extremely high degree of skepticism.

Should Generics face similar issues in the future, the Bureau encourages them to bring any concerns to the Bureau's attention at an early stage.

1. The Inquiry

a. Jinarc and its Risk Management Plan

Jinarc is the only pharmacological therapy approved in Canada for the treatment of autosomal dominant polycystic kidney disease ("**ADPKD**"), a genetic disease in which numerous cysts develop in both kidneys, enlarging them and impairing their function. Jinarc is indicated as a treatment to slow the progression of kidney enlargement and kidney function decline in patients with ADPKD.

Due to the risk of liver injury as a side effect of the drug's use, Jinarc is subject to a Risk Management Plan ("**RMP**"). Jinarc's RMP includes a controlled distribution program, known as the hepatic safety monitoring and distribution programme, which was required by Health Canada prior to marketing the drug. As a result, Jinarc is only available in Canada from Otsuka or its authorized third-party distributor ("**Otsuka's Distributor**").

The Bureau's understanding is that, as of July 25, 2019, no patents or other intellectual property rights applied to Jinarc that would impede the granting of marketing approvals to a generic drug manufacturer.

b. Six-resident application [2]

In October 2019, the Bureau received a six-resident application alleging that Otsuka had restricted a Generic's access to samples of Jinarc necessary to secure regulatory approvals, thereby delaying the marketing of a generic equivalent of Jinarc. The Commissioner initiated an inquiry on October 11, 2019.

The Bureau's inquiry related to Otsuka's treatment of the requests for samples of Jinarc by the Generic. Specifically, the Bureau's inquiry focussed on Otsuka's delay and failure to supply the Generic in response to requests first made to Otsuka's distributor, and later to Otsuka itself, as described more fully below.

On December 12, 2019, the Bureau filed an Application under section 11 of the Act [3] to obtain further information from Otsuka. The Application was adjourned on December 19, 2019, upon condition that Otsuka supply Jinarc to the Generic by end of January 2020, or such later date as the Generic may request. On February 18, 2020, the section 11 application was withdrawn after the Generic confirmed that the supply of Jinarc it had received was sufficient for its purposes, and on March 6, 2020, the Bureau's inquiry was discontinued.

c. Timeline of the alleged conduct

The Bureau's investigation confirmed that, since February 2019, the Generic made numerous attempts to acquire samples of Jinarc from Otsuka's Distributor. The Bureau's understanding is that the Generic's requests were referred to Otsuka by Otsuka's Distributor within a few weeks. Despite these requests, the Generic did not receive the requested samples from Otsuka's Distributor.

The Generic then sought samples of Jinarc from Otsuka directly as of May 2019. Over the course of the summer of 2019, there were various communications between the Generic and Otsuka where Otsuka raised its concerns over supplying Jinarc to the Generic. Otsuka's concerns revolved around the risk minimization measures set out in Jinarc's RMP and whether the supply of samples of Jinarc to the Generic would be in breach of the RMP. Otsuka also indicated that it needed clarification from Health Canada to ensure that the supply of Jinarc complied with Health Canada's guidelines and notice issued on July 4, 2019 (the "**July 2019 Notice**") [4], as detailed below.

During the course of events and prior to the Bureau's involvement in this matter, Health Canada issued the July 2019 Notice to drug manufacturers and sponsors concerning RMPs. The July 2019 Notice clarified that "[e]lements of an RMP, such as controlled distribution programs, cannot restrict access to CRPs for generic drug manufacturers that are conducting comparative testing". Even after the July 2019 Notice was issued, Otsuka maintained that it was unsure whether supply of Jinarc samples to a Generic would be in breach of its obligations under the RMP since Jinarc was subject to what Otsuka viewed as a very stringent RMP.

Despite Otsuka's stated ongoing concerns with supplying Jinarc to the Generic, it is the Bureau's understanding that Otsuka did not take any meaningful steps to seek further clarification from Health Canada until November 2019, months after the Generic initially sought supply of Jinarc samples and only after the Bureau's involvement in this matter. Following Otsuka's discussions and correspondence with Health Canada, Health Canada confirmed to Otsuka in December 2019, that it would not consider it a violation of the RMP for the branded drug manufacturer to provide a Generic with samples of the drug product to perform the necessary comparative testing. Otsuka subsequently committed to providing Jinarc samples to the Generic before the end of January 2020, or such later date as the Generic may request.

2. Analysis

Consistent with the 2018 Position Statement, the Bureau considered these allegations under the abuse of dominance provisions of the Act. Abuse of dominance occurs when a dominant firm or group of firms in a market engages in a practice of anti-competitive acts, with the result that competition has been or is likely to be prevented or lessened substantially. [5]

As the matter was resolved at an early stage of the investigation, it was not necessary for the Bureau to take further action. However, the facts as understood by the Bureau raised serious concerns under the abuse of dominance provision of the Act.

a. Dominance

The Bureau's preliminary view was that the relevant geographic market is national, and the relevant product market is confined to drugs containing tolvaptan for the treatment of ADPKD (i.e., Jinarc and any generic equivalents), consistent with the approach articulated in the Bureau's 2018 Position Statement. In this case, the fact that Jinarc is the only drug approved for the treatment of ADPKD reinforced this product market definition, as there is no pharmaceutical substitute marketed in Canada.

Otsuka is the only drug manufacturer marketing tolvaptan in Canada, and as a result, currently holds a monopoly position in the relevant market. Accordingly, the Bureau's preliminary view is that Otsuka possesses a substantial degree of market power in the relevant market.

b. A practice of anti-competitive acts

The Bureau's preliminary view is that Otsuka appears to have engaged in a practice of anti-competitive acts, in particular given Otsuka's failure to address its stated concerns surrounding supply of Jinarc to a Generic in a timely manner, especially following the issuance of Health Canada's July 2019 Notice.

The Bureau's preliminary view is that it was reasonably foreseeable that Otsuka's delay and failure to supply the Generic would have a negative, exclusionary impact on a competitor. The Bureau considers this indicative of anti-competitive intent, especially as these events occurred after the Bureau made clear that this type of conduct raises concerns under the Act, as detailed in the 2018 Position Statement. Given this evidence of anti-competitive intent,

the Bureau considered potential justifications for Otsuka's conduct, taking into account both Otsuka's stated reasons for delay and its failure to supply samples of Jinarc to the Generic, as well as the timeliness of Otsuka's actions to address its concerns relating to supply.

As stated above, one of Otsuka's stated reasons for not supplying the Generic related to Jinarc's RMP. The Bureau does not find this justification persuasive in light of the issuance and clarity of Health Canada's July 2019 Notice. In any event, even if Otsuka required additional clarity beyond what was contained in the Notice, the information gathered suggests that Otsuka waited months before seeking guidance from Health Canada despite the Generic's repeated requests for samples. In the Bureau's view, this further undermines the stated justification for the refusal to supply.

Because the matter was resolved at an early stage of the investigation, the Bureau did not fully consider additional justifications offered by Otsuka in respect of the delay and failure to supply the Generic with Jinarc, including liability concerns. The Bureau will assess the objective basis for liability and reputational risk concerns in light of the fact that bioequivalence testing protocols are typically reviewed and approved in advance by regulatory authorities to ensure proper safety standards are in place.

c. Substantial lessening or prevention of competition

As a general matter, generic drugs are priced substantially lower than branded drugs and take a significant volume of sales away from the branded drug when they are introduced. Typically, the first generic drug introduced to the market is priced at 85% (or less) of the cost of the branded pharmaceutical. The Bureau has no information to suggest that the first generic tolvaptan product on the market would not also have a similar price reduction from the cost of Jinarc.

There is reason to believe that generic entry was delayed by approximately 11 months compared to if the Generic had received samples upon the first request to Otsuka's Distributor, and would have been delayed longer had adequate supply not been provided soon after the Bureau became aware of the conduct and commenced its inquiry. The Bureau has not fully substantiated the likely price effect or magnitude of delay, but if true, these facts would appear to be consistent with a substantial prevention of competition.

3. Conclusion

The Commissioner has decided to discontinue his inquiry following supply of Jinarc to the Generic by Otsuka. The Bureau notes that the specificity and credible information set out in the six-resident application allowed it to take swift action in this matter, as evidenced by the timely filing of an Application under section 11 to gather further information from Otsuka.

Should another situation arise that suggests evidence of competitive harm resulting from a drug manufacturer's failure to provide access to samples of its branded products to Generics, or any other conduct that excludes competitors, the Bureau will not hesitate to take appropriate action.

Footnotes

1 See Competition Bureau Statement Regarding Its Investigation into Alleged Practices of Celgene, Pfizer, Sanofi dated December 20, 2018.

2 Under section 9 of the Act, any six persons who are residents of Canada and are over the age of 18 may apply to the Commissioner for an inquiry into a matter, often called a six resident application.

3 The Commissioner may apply under section 11 of the Act for an order to obtain information that is relevant to his inquiry.

4 See Health Canada's Notice of clarification to drug manufacturers and sponsors - Risk Management Plans dated July 4, 2019.

5 For more information on the abuse of dominance provisions, see the Bureau's Abuse of Dominance Enforcement Guidelines.

Date modified:
2022-01-20

ontact the Competition Bureau

This is **Exhibit "5"** referred to in the Affidavit sworn remotely by Nick Boorman, stated as being at the City of Toronto, in the Province of Ontario, before me at the City of Toronto, in the Province of Ontario, on September 29, 2023, in accordance with O. Reg. 431/20, *Administering Oath or Declaration Remotely*

A Commissioner, etc.

Exhibit “6”

Notice of Compliance Search Results

From Health Canada

Click on the link to get more details of an individual Notice of Compliance.

New search

Filter items Showing 1 to 7 of 7 entries **Show** 10 **entries**

List of searched Notices of Compliance (NOC)

Product(s)	Manufacturer	Published Notes	Notice of Compliance date	Medicinal ingredient(s)	DIN(s)
ICLUSIG	TAKEDA PHARMACEUTICALS U.S.A., INC.		2022-10-03	PONATINIB HYDROCHLORIDE	00000N/A
ICLUSIG	TAKEDA PHARMACEUTICALS U.S.A., INC.		2022-08-08	PONATINIB	02437341, 02437333
ICLUSIG	ARIAD PHARMACEUTICALS INC		2019-08-16	PONATINIB HYDROCHLORIDE	00000N/A
ICLUSIG	ARIAD PHARMACEUTICALS INC		2019-06-21	PONATINIB HYDROCHLORIDE	00000N/A
ICLUSIG	ARIAD PHARMACEUTICALS INC		2018-12-12	PONATINIB HYDROCHLORIDE	00000N/A
ICLUSIG	ARIAD PHARMACEUTICALS INC		2018-03-08	PONATINIB HYDROCHLORIDE	00000N/A
ICLUSIG	ARIAD PHARMACEUTICALS INC	CONDITIONS WERE MET OCTOBER 3, 2022	2015-04-02	PONATINIB HYDROCHLORIDE	02437333, 02437341

Exhibit

New search

Application information

- Search tips
- Notice of Compliance terminology
- Frequently asked questions

Related information

- Notice of Compliance listings
- MedEffect Canada
- Adverse Drug Reaction - veterinary drugs
- Drug Product Database

Contact us

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Date modified: 2022-11-25

This is **Exhibit "6"** referred to in the Affidavit sworn remotely by Nick Boorman, stated as being at the City of Toronto, in the Province of Ontario, before me at the City of Toronto, in the Province of Ontario, on September 29, 2023, in accordance with O. Reg. 431/20, *Administering Oath or Declaration Remotely*

A Commissioner, etc.

Exhibit "7"

Takeda Completes Acquisition of ARIAD Pharmaceuticals, Inc.

February 16, 2017

Share

– Significantly Enhances Takeda's Global Oncology Portfolio

– Accretive to FY2018 Underlying Core Earnings

– Reinforces Takeda's Commitment to Developing Medicines for Patients Living with Cancer

Takeda Pharmaceutical Company Limited (TSE: 4502) ("Takeda") today announced the completion of its acquisition of ARIAD Pharmaceuticals, Inc. (NASDAQ: ARIA) ("ARIAD") for $24.00 per share in cash.

"We are very pleased to have completed the acquisition of ARIAD Pharmaceuticals. The addition of ARIAD's innovative targeted therapies and research and development capabilities strengthens and diversifies our oncology business, positioning Takeda for sustainable long-term growth in this priority therapeutic area," said Christophe Weber, president and chief executive officer of Takeda. "We are particularly excited by the global potential of brigatinib, an investigational drug product, which we believe will become a best-in-class ALK inhibitor for non-small cell lung cancer with the potential to achieve peak annual sales of over $1 billion. We are also impressed with the swiftness and agility of Takeda and ARIAD employees as they have planned for a successful integration while remaining focused on strategic goals. This bodes very well for the future of our combined business,

and we look forward to building on this strong start to maximize the benefit of Iclusig®(ponatinib) and potential of brigatinib for cancer patients."

"The acquisition of ARIAD is transformational for Takeda Oncology. Iclusig enhances our strong position in hematology in the U.S., and brigatinib has the potential to broaden our solid tumor franchise globally," said Christophe Bianchi, president of Takeda Oncology. "There is a strong cultural fit between our two companies, with a shared mission to advance innovative therapies to improve the lives of patients with cancer. We have been working together over the past month to plan for a smooth integration of our businesses and we will work closely with regulatory authorities on our brigatinib market authorization submissions."

Takeda continues to expect the transaction to be accretive to Underlying Core Earnings by FY2018. Strong revenue growth and synergy savings will offset increased sales and marketing costs for the anticipated brigatinib launch.

Tender Offer Details

Takeda completed the acquisition through a tender offer and subsequent merger of ARIAD with Kiku Merger Co., Inc., a wholly owned subsidiary of Takeda Pharmaceuticals U.S.A. ARIAD is now an indirect wholly owned subsidiary of Takeda.

The tender offer for all of the outstanding shares of ARIAD common stock expired as scheduled, immediately following the offer's expiration time of 11:59 p.m., Eastern Time, on February 15, 2017. Computershare Trust Company, N.A., the depositary and paying agent for the tender offer, has advised Takeda that 158,558,628 shares of ARIAD common stock were tendered, representing approximately 81.4% of the shares outstanding. All of the conditions to the tender offer having been satisfied, Takeda's indirect wholly owned subsidiary Kiku Merger Co., Inc. has accepted for payment and will promptly pay for all shares tendered. The transaction will be funded by approximately $3.5 billion of new debt and the remainder from existing cash. Takeda is expected to remain investment grade and the transaction has no impact on Takeda's dividend policy.

On February 16, 2017, Takeda completed its acquisition of ARIAD through the merger of Kiku Merger Co., Inc. with ARIAD without a vote of ARIAD's shareholders pursuant to Section 251(h) if the Delaware General Corporation Law. As a result of the merger, ARIAD became an indirect wholly owned subsidiary of Takeda. In connection with the merger, all ARIAD shares not purchased in the tender offer have been converted into the right to receive $24.00 per share in cash, without interest (less any required withholding taxes), the same amount paid for all shares validly tendered and not validly withdrawn in the tender offer. ARIAD common stock will cease to be traded on the NASDAQ Global Select Market.

Evercore Partners acted as financial advisor and Cleary Gottlieb Steen & Hamilton LLP acted as legal advisor to Takeda. J.P. Morgan Securities LLC, Goldman, Sachs & Co. and Lazard acted as financial advisors and Paul, Weiss, Rifkind, Wharton & Garrison LLP acted as legal advisor to ARIAD.

About Takeda Pharmaceutical Company

Takeda Pharmaceutical Company Limited is a global, research and development-driven pharmaceutical company committed to bringing better health and a brighter future to patients by translating science into life-changing medicines. Takeda focuses its R&D efforts on oncology, gastroenterology and central nervous system therapeutic areas plus vaccines. Takeda conducts R&D both internally and with partners to stay at the leading edge of innovation. New innovative products, especially in oncology and gastroenterology, as well as our presence in Emerging Markets, fuel the growth of Takeda. More than 30,000 Takeda employees are committed to improving quality of life for patients, working with our partners in health care in more than 70 countries. Additional information about Takeda is available through its corporate website, www.Takeda.com.

Please see Iclusig® (ponatinib) full Prescribing Information, including Boxed Warning.

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Cautionary Statement Regarding Forward-Looking Statements

This press release contains forward-looking statements. When used in this press release, the words “can,” “will,” “believes,” “intends,” “expects,” “is expected,” similar expressions and any other statements that are not historical facts are intended to identify those assertions as forward-looking statements. Such statements are based on a number of assumptions that could ultimately prove inaccurate, and are subject to a number of risks. Neither Takeda nor ARIAD assumes any obligation to update any forward-looking statement, whether as a result of new information, future events or otherwise, unless required by law.

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Financial Highlights

HCPs

Patients

This website provides information about Takeda's worldwide business. For specific information about our local markets, please use the country selector.

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This is **Exhibit "7"** referred to in the Affidavit sworn remotely by Nick Boorman, stated as being at the City of Toronto, in the Province of Ontario, before me at the City of Toronto, in the Province of Ontario, on September 29, 2023, in accordance with O. Reg. 431/20, *Administering Oath or Declaration Remotely*

A Commissioner, etc.

Exhibit “8”

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrICLUSIG®

Ponatinib Tablets

Tablets, 15 mg and 45 mg (as ponatinib hydrochloride), oral

Protein-tyrosine kinase inhibitor

ATC code: L01EA05

Takeda Pharmaceuticals U.S.A., Inc.
95 Hayden Ave.
Lexington, MA, United States
02421

Date of Initial Authorization:
MAR 31, 2015

Date of Revision:
OCT 03, 2022

Imported and distributed by:
Paladin Labs Inc.,
Saint-Laurent, QC
H4M 2P2

Submission Control Number: 258641

RECENT MAJOR LABEL CHANGES

3 Serious Warnings and Precautions Box	10/2022
4.1 Dosing Considerations	10/2022
4.2 Dosage and Administration	10/2022
7 Warnings and Precautions	10/2022
7 Warnings and Precautions, 7.1.1 Pregnant Women	10/2022
7 Warnings and Precautions, 7.1.4 Geriatrics	10/2022
7 Warnings and Precautions, 7.1.8 Renal Impairment	10/2022

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ICLUSIG (ponatinib tablets) is indicated for:

- the treatment of adult patients with chronic phase (CP), accelerated phase (AP), or blast phase (BP) chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom other tyrosine kinase inhibitor (TKI) therapy is not appropriate, including CML or Ph+ ALL that is T315I mutation positive or where there is prior TKI resistance or intolerance.

ICLUSIG Controlled Distribution Program

ICLUSIG is only available through a controlled program referred to as the **ICLUSIG Controlled Distribution Program**. Under this program, only prescribers who have completed the certification and are registered with the program are able to prescribe ICLUSIG. Trained pharmacies will verify the prescriber's certified status prior to dispensing ICLUSIG to the patient. For further information about the program, please call 1-888-867-7426 (English and French) or visit www.iclusigcdp.ca.

A Patient Alert/Wallet Card describing the Serious Warnings and Precautions will be distributed to the patient (or included in packaging) at the time of dispensing and renewal. A copy of this information is on the last page of the product monograph.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Compared to patients < 65 years, older patients (with CP-CML) are more likely to experience adverse reactions.

Evidence from the clinical study suggests that use in the geriatric population (with CP-CML) is associated with reduced safety and effectiveness (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

- ICLUSIG is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- Do not use in patients with unmanaged cardiovascular risk factors, including uncontrolled hypertension. Hypertension may contribute to the risk of arterial occlusive events (AOEs). Blood pressure should be monitored and managed to avoid hypertension (see also 7 WARNINGS AND PRECAUTIONS, Hypertension and Monitoring and Laboratory Tests).

- Do not use in patients who are not adequately hydrated and with uncorrected high uric acid levels (see 7 WARNINGS AND PRECAUTIONS, Tumour Lysis Syndrome).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

ICLUSIG should only be prescribed and monitored by a physician who has completed the certification with the **ICLUSIG Controlled Distribution Program** and who is experienced in the use of antineoplastic therapy and in the treatment of CML or Ph+ ALL.

- AOEs, including fatalities, occurred in ICLUSIG-treated patients. AOEs included fatal myocardial infarction, fatal cerebral infarction, fatal mesenteric artery occlusion, disseminated intravascular coagulation, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, sometimes resulting in amputation, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients 50 years or younger, experienced these events. Monitor for evidence of AOEs. Interrupt or discontinue ICLUSIG immediately in case of an AOE. Consider benefit-risk to guide a decision to restart ICLUSIG (see 4.2 Recommended Dose and Dosage Adjustment, 7 WARNINGS AND PRECAUTIONS, Arterial Occlusive Events).
- Venous thromboembolic events (VTEs) occurred in ICLUSIG-treated patients. Cases of pulmonary embolism have been reported, some of which were fatal. Monitor for evidence of VTEs. Interrupt or discontinue ICLUSIG immediately in case of a VTE (see 4.2 Recommended Dose and Dosage Adjustment, 7 WARNINGS AND PRECAUTIONS, Venous Thromboembolic Events).
- Heart failure (some fatal), including left ventricular dysfunction and ejection fraction decrease, occurred in ICLUSIG-treated patients. Monitor for signs or symptoms consistent with heart failure and treat as clinically indicated. Interrupt or discontinue ICLUSIG in patients who develop new or worsening serious heart failure (see 4.2 Recommended Dose and Dosage Adjustment, 7 WARNINGS AND PRECAUTIONS, Heart Failure and Left Ventricular Dysfunction).
- Hemorrhage events (some fatal), including intracranial hemorrhage, hemorrhagic gastritis, and hemorrhagic cerebral infarction occurred in ICLUSIG-treated patients. Most hemorrhagic events, but not all, occurred in patients with grade 3 or 4 thrombocytopenia. Interrupt or discontinue ICLUSIG in patients with serious or severe hemorrhage (see 4.2 Recommended Dose and Dosage Adjustment, 7 WARNINGS AND PRECAUTIONS, Hemorrhage).
- Hepatotoxicity (including fatal acute hepatic failure) has been reported. Monitor hepatic function prior to and during treatment. Interrupt or discontinue ICLUSIG in patients with hepatotoxicity (see 7 WARNINGS AND PRECAUTIONS, Hepatotoxicity and 4.2 Recommended Dose and Dosage Adjustment).
- Myelosuppression (thrombocytopenia, neutropenia, and anemia) has been reported in ICLUSIG-treated patients. Myelosuppression was managed by withholding ICLUSIG temporarily or reducing the dose (see 4.2 Recommended Dose and Dosage Adjustment, 7 WARNINGS AND PRECAUTIONS, Myelosuppression).
- Pancreatitis and elevations in serum lipase or amylase have been reported. Dose modification may be required (see 4.2 Recommended Dose and Dosage Adjustment, 7 WARNINGS AND PRECAUTIONS, Pancreatitis and Serum Lipase).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

ICLUSIG must only be prescribed and used in treatment initiated by a physician who has completed certification with the **ICLUSIG Controlled Distribution Program**, and who is experienced in diagnosing patients with leukemia (in particular, CML or Ph+ ALL) and with treatments including antineoplastic therapy.

Before starting treatment with ICLUSIG, the cardiovascular status of the patient should be assessed and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored and therapy optimized during treatment with ICLUSIG.

Monitoring for evidence of AOEs and VTEs should be performed and ICLUSIG should be interrupted or discontinued immediately in case of vascular occlusion (see Table 1).

Hematologic support such as platelet transfusion and hematopoietic growth factors can be used during treatment if clinically indicated.

Avoid co-administration of ICLUSIG with strong CYP3A inhibitors and strong CYP3A inducers. See 9.4 Drug-Drug Interactions.

Advise patients to take ICLUSIG exactly as prescribed and not to change their dose or to stop taking ICLUSIG unless they are told to do so by their healthcare provider.

Advise patients who have intolerance to lactose that ICLUSIG contains lactose (see 7.1.6 Lactose Intolerance).

4.2 Recommended Dose and Dosage Adjustment

CP-CML

The recommended starting dosage of ICLUSIG is 45 mg orally once daily with a reduction to 15 mg orally once daily upon achievement of molecular response (≤1% BCR-ABL1^{IS}). Patients with loss of response can re-escalate the dose of ICLUSIG to a previously tolerated dosage of 30 mg or 45 mg orally once daily. Continue ICLUSIG until loss of response at the re-escalated dose or unacceptable toxicity. Consider discontinuing ICLUSIG if hematologic response has not occurred by 3 months.

AP-CML, BP-CML, and Ph+ ALL

The recommended starting dosage is 45 mg of ICLUSIG once daily. Continue ICLUSIG until loss of response or unacceptable toxicity. Consider reducing the dose of ICLUSIG for patients with accelerated phase (AP) CML who have achieved a major cytogenetic response. Consider discontinuing ICLUSIG if response has not occurred by 3 months.

Health Canada has not authorized an indication for pediatric use.

Dose Modifications for Adverse Reactions

Recommendations for dose modifications of ICLUSIG for the management of adverse reactions are summarized in Table 1 and recommended dose reductions of ICLUSIG for adverse reactions are presented in Table 2. For a dose of 30 mg or 15 mg once daily, 15 mg tablets are available.

Table 1. Recommended ICLUSIG Dose Modifications for Adverse Reactions

Adverse Reaction	Severity	ICLUSIG Dose Modification
AOE: cardiovascular or cerebrovascular	Grade 1	Interrupt ICLUSIG until resolved, then resume at same dose.
	Grade 2	Interrupt ICLUSIG until ≤ Grade 1, then resume at next lower dose. Discontinue ICLUSIG if recurrence.
	Grade 3 or Grade 4	Discontinue ICLUSIG.
AOE: peripheral vascular and other **or** **VTE**	Grade 1	Interrupt ICLUSIG until resolved, then resume at same dose.
	Grade 2	Interrupt ICLUSIG until ≤ Grade 1, then resume at same dose. If recurrence, interrupt ICLUSIG until ≤ Grade 1, then resume at next lower dose.
	Grade 3	Interrupt ICLUSIG until ≤ Grade 1, then resume at next lower dose. Discontinue ICLUSIG if recurrence.
	Grade 4	Discontinue ICLUSIG.
Heart Failure	Grade 2 or 3	Interrupt ICLUSIG until ≤ Grade 1, then resume at next lower dose. Discontinue ICLUSIG if recurrence.
	Grade 4	Discontinue ICLUSIG.
Hepatic Toxicity	AST or ALT greater than 3 times ULN	Interrupt ICLUSIG until ≤ Grade 1, then resume at next lower dose.
	AST or ALT at least 3 times ULN concurrent with bilirubin greater than 2 times ULN and alkaline phosphatase less than 2 times ULN	Discontinue ICLUSIG.
Pancreatitis and Elevation of Lipase / Amylase	Asymptomatic Grade 2 pancreatitis and/or Grade 2 elevation of lipase/amylase	Consider interrupting ICLUSIG until resolution then resume at same dose.

Adverse Reaction	Severity	ICLUSIG Dose Modification
	Grade 3 or 4 asymptomatic elevation of lipase/amylase (> 2.0 × ULN) only	Interrupt ICLUSIG until ≤ Grade 1 (less than 1.5 times ULN) then resume at next lower dose.
	Grade 3 pancreatitis	Interrupt ICLUSIG until complete resolution of symptoms and after recovery of lipase elevation ≤ Grade 1, then resume at next lower dose.
	Grade 4 pancreatitis	Discontinue ICLUSIG
Myelosuppression	ANC less than 1.0×10^9/L or platelets less than 50×10^9/L	Interrupt ICLUSIG until ANC at least 1.5×10^9/L and platelets at least 75×10^9/L, then resume at same dose. If recurrence, interrupt ICLUSIG until resolution, then resume at next lower dose.
Other Non-hematologic Adverse Reactions	Grade 2	Interrupt ICLUSIG until ≤ Grade 1, then resume at same dose. If recurrence, interrupt ICLUSIG until ≤ Grade 1, then resume at next lower dose.
	Grade 3 or 4	Interrupt ICLUSIG until ≤ Grade 1, then resume at next lower dose. Discontinue ICLUSIG if recurrence.

Grading based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0.
ANC = absolute neutrophil count; AOE = arterial occlusive event; ULN = upper limit of normal; VTE = venous thromboembolic event

Table 2. Recommended Dose Reductions for ICLUSIG for Adverse Reactions

Dose Reduction	Dosage for Patients with CP-CML	Dosage for Patients with AP-CML, BP-CML, and Ph+ ALL
First	30 mg orally once daily	30 mg orally once daily
Second	15 mg orally once daily	15 mg orally once daily
Subsequent Reduction	Permanently discontinue ICLUSIG in patients unable to tolerate 15 mg orally once daily.	Permanently discontinue ICLUSIG in patients unable to tolerate 15 mg orally once daily.

Hepatic Impairment

ICLUSIG has not been studied at doses above 30 mg in patients with hepatic impairment (Child-Pugh A, B and C). Caution is recommended when administering ICLUSIG to patients with hepatic impairment. The recommended starting dose is 30 mg once daily in patients with hepatic impairment (see 7.1.7 Hepatic Impairment).

Renal Impairment

ICLUSIG has not been studied in patients with severe renal impairment (creatinine clearance <30 mL/min). Caution is recommended when administering ICLUSIG to patients with severe renal impairment or end-stage renal disease (see 7.1.8 Renal Impairment).

Mild to moderate renal impairment (creatinine clearance 30 to 89 mL/min) did not have a clinically meaningful effect on the pharmacokinetics of ponatinib based on a population pharmacokinetic analysis.

4.4 Administration

ICLUSIG tablets should be swallowed whole. Patients should not crush or dissolve the tablets. ICLUSIG may be administered with or without food.

4.5 Missed Dose

If a dose is missed, the patient should not take an additional dose. In this case, the patient should take the usual dose at the next scheduled time.

5 OVERDOSAGE

Isolated cases of unintentional overdose with ICLUSIG were reported in clinical trials. Single doses of 165 mg and an estimated 540 mg in 2 patients did not result in any clinically significant adverse reactions. Multiple doses of 90 mg per day for 12 days in a patient resulted in pneumonia, systemic inflammatory response, atrial fibrillation, and asymptomatic, moderate pericardial effusion. Treatment was interrupted, the events resolved, and ICLUSIG was restarted at 45 mg, once daily. Multiple doses of 60 mg per day, administered due to lack of efficacy, in a Ph+ ALL patient resulted in hospitalization for pleural and pericardial effusions after 6 days of treatment. The patient was treated with diuretics and the events abated. ICLUSIG dosing was not interrupted.

There is no specific antidote for overdose with ICLUSIG. In the event of an overdose, the patient should be observed and appropriate supportive treatment given.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 15 mg and 45 mg	Tablet core: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium starch glycolate Tablet coating: polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide (E171)

15 mg: Each tablet contains 15 mg ponatinib (as 16.03 mg ponatinib hydrochloride). The 15 mg tablet is a white, biconvex, round film-coated tablet that is approximately 6 mm in diameter, with "A5" debossed on one side. Supplied in HDPE bottles with screw-top closures containing 60 tablets and one canister desiccant.

45 mg: Each tablet contains 45 mg of ponatinib (as 48.08 mg ponatinib hydrochloride). The 45 mg tablet is a white, biconvex, round film-coated tablet that is approximately 9 mm in diameter, with "AP4" debossed on one side. Supplied in HDPE bottles containing 30 tablets and one canister desiccant.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Avoid co-administration of ICLUSIG with strong CYP3A inhibitors. A reduction of the starting dose of ICLUSIG is recommended with concurrent use of ICLUSIG and strong CYP3A inhibitors (see 9.4 Drug-Drug Interactions).

Carcinogenesis and Mutagenesis

A statistically significant increased incidence of squamous cell carcinoma of the clitoral gland in rats was observed at a plasma exposure level lower or equal to the human exposure within the clinically recommended dose range. The clinical relevance of this finding is not known (see 16 NON-CLINICAL TOXICOLOGY).

Cardiovascular

Before starting treatment with ICLUSIG, the cardiovascular status of the patient should be assessed and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored and therapy optimized during treatment with ICLUSIG (see 9.4 Drug-Drug Interactions and 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Hypertension may contribute to the risk of AOEs. Blood pressure should be monitored and managed to avoid hypertension (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Arterial Occlusive Events

In clinical trials arterial occlusive events (AOEs), including cardiovascular (e.g., fatal myocardial infarction, acute coronary syndrome), cerebrovascular (e.g., fatal cerebral infarction, stroke, stenosis of large arterial vessels of the brain), and peripheral vascular (e.g., retinal occlusion leading to vision loss, peripheral arterial occlusive disease, sometimes resulting in amputation) occlusions, some requiring the need for urgent revascularization procedures (cerebrovascular, coronary, and peripheral arterial), occurred in ICLUSIG-treated patients with and without cardiovascular risk factors (including patients less than 50 years old). Some patients experienced recurrent or multisite vascular occlusion. Renal artery stenosis, associated with worsening, labile or treatment-resistant hypertension, has also occurred in some ICLUSIG-treated patients.

In PACE, patients with uncontrolled hypertriglyceridemia and patients with clinically significant or active cardiovascular disease, including any history of clinically significant atrial/ventricular arrhythmias or history of myocardial infarction, unstable angina, or congestive heart failure within the 3 months prior to the first dose of ICLUSIG, were excluded. In OPTIC, patients with uncontrolled hypertension or

diabetes and patients with clinically significant, uncontrolled, or active cardiovascular disease, including any history of myocardial infarction, peripheral vascular infarction, revascularization procedure, congestive heart failure, venous thromboembolism, or clinically significant atrial/ventricular arrhythmias, were excluded. Consider whether the benefits of ICLUSIG are expected to exceed the risks.

In the PACE trial, AOEs occurred in 25% (111/449) of ICLUSIG-treated patients with some patients experiencing events of more than one type. Cardiovascular AOEs, including fatal and life-threatening myocardial infarction and coronary artery occlusion occurred in 13% (59/449) of ICLUSIG-treated patients. Patients developed heart failure concurrent or subsequent to the myocardial ischemic event. Cerebrovascular AOEs, including fatal stroke, occurred in 9% (41/449) of ICLUSIG-treated patients. ICLUSIG has been associated with stenosis over multiple segments in major arterial vessels that supply the brain (e.g., carotid, vertebral, middle cerebral artery). Peripheral AOEs, including fatal mesenteric artery occlusion and life-threatening peripheral arterial disease occurred in 11% (48/449) of ICLUSIG-treated patients. Patients have developed digital or distal extremity necrosis and have required amputations.

In the OPTIC trial, arterial occlusion occurred in 10% (9/94) of ICLUSIG-treated patients who received a starting dose of 45 mg. Of these 9 patients, 4%, 2%, and 3% experienced a cardiovascular, cerebrovascular, and peripheral vascular AOE, respectively.

In PACE, the median time to onset of AOEs was 13.4 months overall (range 3 days to 59.7 months) and 15.4 months in CP-CML patients. AOEs were more frequent with increasing age and in patients with prior history of ischemia, hypertension, diabetes, or hyperlipidemia. In OPTIC (CP-CML patients), the median time to onset of AOEs was 6.4 months for the 45 mg cohort.

ICLUSIG should not be used in patients with a history of myocardial infarction, prior revascularization or stroke unless the potential benefit of treatment outweighs the potential risk (see 2 CONTRAINDICATIONS).

Before starting treatment with ICLUSIG, the cardiovascular status of the patient should be assessed and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored during treatment with ICLUSIG (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). If decreased vision or blurred vision occurs, an ophthalmic examination (including fundoscopy) should be performed and ICLUSIG should be interrupted if arterial occlusion is suspected. Monitoring for evidence of arterial occlusion should be performed and ICLUSIG should be interrupted immediately in case of arterial occlusion. A benefit–risk consideration should guide a decision to restart ICLUSIG therapy (see 4.2 Recommended Dose and Dosage Adjustment).

Inform patients that serious arterial occlusive events (including arterial stenosis sometimes requiring revascularization) have occurred. Advise patients to immediately seek medical attention with any symptoms suggestive of a blood clot such as chest pain, shortness of breath, weakness on one side of the body, speech problems, leg pain, or leg swelling.

Venous Thromboembolic Events

Venous thromboembolic events (VTEs) occurred in ICLUSIG-treated patients.

In the PACE trial, 6% (27/449) of ICLUSIG-treated patients experienced VTEs, including deep vein thrombosis, pulmonary embolism, superficial thrombophlebitis, retinal vein occlusion, and retinal vein thrombosis with vision loss.

Cases of pulmonary embolism have been reported, some of which were fatal. The incidence of thromboembolic events is higher in patients with Ph+ ALL or BP-CML than those with AP-CML or CP-CML.

Of the 94 patients who received a starting dose of 45 mg in OPTIC, 1 patient experienced a VTE (Grade 1 retinal vein occlusion).

If decreased vision or blurred vision occurs, an ophthalmic examination (including fundoscopy) should be performed and ICLUSIG should be interrupted if a VTE is suspected. Monitoring for evidence of a venous thromboembolism should be performed and ICLUSIG should be interrupted immediately in case of a VTE. A benefit-risk consideration should guide a decision to restart ICLUSIG therapy (see 4.2 Recommended Dose and Dosage Adjustment).

Inform patients that serious VTEs have occurred. Advise patients to immediately seek medical attention with any symptoms suggestive of a blood clot such as chest pain, cough, fever, shortness of breath, feeling faint, weakness on one side of the body, speech problems, leg pain or leg swelling, rapid breathing or irregular heartbeat.

Heart Failure and Left Ventricular Dysfunction

Heart failure or left ventricular dysfunction, including fatal cases, occurred in ICLUSIG-treated patients (see 8 ADVERSE REACTIONS and 10.2 Pharmacodynamics).

Left ventricular ejection fraction (LVEF) should be evaluated in all patients prior to initiation of treatment with ICLUSIG, at three months after initiation of ICLUSIG, and whenever clinically indicated. ICLUSIG should be used with caution in patients with a history of congestive heart failure or conditions that could impair left ventricular function. Patients receiving ICLUSIG should be monitored for signs and symptoms consistent with congestive heart failure, with treatment as clinically indicated, including interruption of ICLUSIG. Consider dose modification or discontinuation of ICLUSIG in patients who develop new or worsening-serious heart failure (see 4.2 Recommended Dose and Dosage Adjustment).

In PACE, 39 of 449 patients (9%) experienced heart failure or left ventricular dysfunction, including 28 patients (6%) with serious events and 4 patients (1%) with fatal events.

In OPTIC, 3 of 94 patients (3%) in the 45 mg cohort experienced heart failure (left ventricular dysfunction, heart failure, or ejection fraction decreased).

Inform patients of the possibility of heart failure and abnormally slow or fast heart rates. Advise patients to contact their healthcare provider if they experience symptoms such as shortness of breath, chest pain, palpitations, dizziness, or fainting.

Hypertension

Hypertension (including hypertensive crisis) occurred in ICLUSIG-treated patients. Patients may require urgent clinical intervention. Hypertension may contribute to the risk of AOEs, including renal artery stenosis. During ICLUSIG treatment, blood pressure should be monitored and managed. Hypertension should be treated to normalize blood pressure. ICLUSIG treatment should be temporarily interrupted, dose reduced or stopped if hypertension is not medically controlled. Monitoring for significant or unexplained hypertension is recommended as it may contribute to renal vascular disease. In the event of significant worsening, labile or treatment-resistant hypertension, interrupt treatment and consider evaluating for renal artery stenosis.

In PACE, hypertension was observed in 32% (142/449) of patients (12% grade 3 or greater); hypertensive crisis was observed in two patients (<1%). Eight patients (2%) experienced treatment-emergent symptomatic hypertension as a serious adverse reaction.

In the 45 mg cohort of OPTIC, 32% (30/94) patients experienced a hypertension event. Two patients (2%) in the 45 mg cohort experienced hypertension as a serious adverse reaction, including hypertensive crisis.

Serious cases of artery dissection have been reported in patients using Vascular Endothelial Growth Factor Receptors (VEGFR) TKIs, including ICLUSIG, with or without hypertension.

Inform patients of the possibility of new or worsening of existing hypertension. Advise patients to contact their healthcare provider for elevated blood pressure or if symptoms of hypertension occur including confusion, headache, dizziness, chest pain, or shortness of breath.

Cardiac Arrhythmias

In PACE, arrhythmia adverse events occurred in 20% (89/449; 7% [33/449] grade 3 or greater) of ICLUSIG-treated patients. Atrial fibrillation was the most common arrhythmia and occurred in 8% (34/449) of patients, approximately half of which were grade 3 or 4. Other grade 3 or 4 arrhythmia events included syncope (9 patients; 2%), tachycardia and bradycardia (2 patients each; <1%), and electrocardiogram QT prolonged, atrial flutter, supraventricular tachycardia, ventricular tachycardia, atrial tachycardia, atrioventricular block complete, cardio-respiratory arrest, loss of consciousness, and sinus node dysfunction (1 patient each; <1%).

Symptomatic bradyarrhythmias that led to a requirement for pacemaker implantation occurred in 1% (3/449) of ICLUSIG-treated patients. The cardiac rhythms (1 case each) identified were complete heart block, sick sinus syndrome, and atrial fibrillation with bradycardia and pauses.

In the 45 mg cohort of OPTIC, 16% (15/94) of patients experienced cardiac arrhythmias (6% grade 3-4); the most common were atrial fibrillation and tachycardia (2% each).

Advise patients to report signs and symptoms suggestive of slow heart rate (fainting, dizziness) or rapid heart rate (chest pain, palpitations, dizziness). Interrupt ICLUSIG and evaluate.

Fluid Retention

In PACE, fluid retention adverse events occurred in 32% (4% grade 3 or greater) of patients treated with ICLUSIG. These events included peripheral edema, pericardial effusion, and pleural effusion.

Of the 94 patients in the 45 mg cohort in OPTIC, 5% patients experienced fluid retention adverse events. The most frequent fluid retention events were peripheral edema and pleural effusion.

Patients should be monitored for fluid retention. Interrupt, reduce or discontinue ICLUSIG as clinically indicated. Inform patients of the possibility of developing fluid retention and to contact their healthcare provider for symptoms such as leg swelling, abdominal swelling, weight gain, or shortness of breath.

Driving and Operating Machinery

The effect of ICLUSIG on the ability to drive or operate machinery was not specifically measured; however, in clinical studies with ICLUSIG, visual impairment, blurred vision, dizziness, mental status changes, and confusion were reported. Patients should be advised not to drive or operate machinery if they experience any of these symptoms while taking ICLUSIG.

Gastrointestinal

Gastrointestinal Perforation and Impaired Wound Healing

Serious gastrointestinal perforation (fistula) was reported in a patient 38 days following cholecystectomy. ICLUSIG may impair wound healing based on the mechanism of action. Temporary interruption of ICLUSIG therapy should be considered in patients prior to undergoing major surgical procedures. Clinical judgment of adequate wound healing should guide the decision to resume ICLUSIG treatment after surgery.

Advise patients to inform their healthcare provider if they plan to undergo a surgical procedure or had recent surgery. Inform patients that cases of gastrointestinal perforation have been reported.

Hematologic

Hemorrhage

Hemorrhage occurred in 28% (126/449) of ICLUSIG-treated patients in PACE. Severe hemorrhage events, including fatalities, occurred in 7% (32/449) of ICLUSIG-treated patients. The incidence of severe bleeding events was higher in patients with AP-CML, BP-CML, or Ph+ ALL than CP-CML. Gastrointestinal hemorrhage (one fatal) and subdural hematoma (one fatal) were the most commonly reported severe bleeding events (1% each). Most hemorrhagic events, but not all, occurred in patients with grade 3 or 4 thrombocytopenia.

Hemorrhage occurred in 12% (2% grade 3 or greater) of ICLUSIG-treated patients from OPTIC (45 mg cohort).

Interrupt ICLUSIG for serious or severe (grade 3 or greater) hemorrhage and evaluate (discontinuation may be required) (see 4.2 Recommended Dose and Dosage Adjustment).

Inform patients of the possibility of serious bleeding and to immediately contact their healthcare provider with any signs or symptoms suggestive of hemorrhage such as unusual bleeding or easy bruising.

Myelosuppression

Myelosuppression was reported as an adverse event in 60% (269/449) of patients (51% grade 3 or greater) in patients treated with ICLUSIG in PACE. Most commonly reported events included neutropenia, thrombocytopenia, and anemia, occurring in 25%, 44%, and 25% of patients, respectively. Severe (grade 3 or greater) events of thrombocytopenia (36%, 160/449), neutropenia (23%, 101/449) and anemia (16%, 73/449) were reported**.** The incidence of these events was higher in patients with AP-CML or BP-CML/Ph+ ALL than in patients with CP-CML. Of the patients who developed grade 3 or 4 platelet count decreased, most developed it within the first 3 months of treatment.

Myelosuppression events were reported in 63% of ICLUSIG-treated patients from OPTIC (45 mg cohort) of which 43% were grade 3 or greater. Most commonly reported events included neutropenia, thrombocytopenia, and anemia occurring in 30%, 44% and 21% of ICLUSIG-treated patients, respectively.

A complete blood count should be performed every 2 weeks for the first 3 months and then monthly or as clinically indicated. Dose modification may be required. Myelosuppression was generally reversible and was usually managed by withholding ICLUSIG temporarily or reducing the dose (see 4.2 Recommended Dose and Dosage Adjustment).

Myelosuppression was reported in patients with normal baseline laboratory values as well as in patients with pre-existing laboratory abnormalities. In PACE, discontinuation due to myelosuppression occurred due to thrombocytopenia (4%), neutropenia and anemia (<1% each).

Inform patients of the possibility of developing low blood cell counts and to immediately report should fever develop, particularly in association with any suggestion of infection.

Hepatic/Biliary/Pancreatic

Hepatotoxicity

Hepatotoxicity, including acute fatal hepatic failure, occurred in ICLUSIG-treated patients within 1 week of starting ICLUSIG treatment. In PACE, 30% (134/449) of ICLUSIG-treated patients experienced hepatotoxicity events; 11% (51/449) were grade 3 or 4. The most common forms of hepatotoxicity (≥2%) were elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), bilirubin, alkaline phosphatase, and hypoalbuminemia. The incidence of adverse events of ALT and AST elevation was 19% (83/449) and 16% (72/449), respectively. Most patients who reported an event of hepatotoxicity had their first event in the first year of treatment.

In OPTIC (45 mg cohort), 26/94 patients (28%) experienced hepatotoxicity, including 6 patients (6%) with grade 3 or greater. The most frequently reported events of hepatotoxicity (≥2%) in the 45 mg cohort were elevations of ALT, AST, alkaline phosphatase, GGT and transaminases.

Liver function tests (LFTs), including transaminases, should be performed at baseline, then at least monthly or as clinically indicated. Dose interruption, reduction or discontinuation may be required (see 4.2 Recommended Dose and Dosage Adjustment).

Inform patients of the possibility of developing liver function abnormalities and serious hepatic toxicity. Advise patients to immediately seek medical attention if signs of liver failure occur, including yellowing of the eyes or skin, “tea-coloured” urine, or drowsiness.

Pancreatitis and Serum Lipase

In PACE, ICLUSIG was associated with pancreatitis and acute pancreatitis (7%; 6% grade 3 or greater). Elevations of serum lipase and amylase were 39% (14% grade 3 or greater) and 18% (4% grade 3 or greater), respectively. The frequency of pancreatitis is greater in the first 2 months of ICLUSIG use.

Of the 94 patients who received a starting dose of 45 mg in OPTIC, pancreatitis and acute pancreatitis occurred in 2% of patients (2% grade 3 or greater). Elevations of serum lipase and amylase have been reported in 34% (12% grade 3 or greater) and 11% (3% grade 3 or greater) of patients, respectively.

Check serum lipase and amylase every 2 weeks for the first 2 months and then periodically thereafter or as clinically indicated. Dose modification may be required (see Table 1 in 4.2 Recommended Dose and Dosage Adjustment). If lipase elevations are accompanied by abdominal symptoms, ICLUSIG should be withheld and patients evaluated for evidence of pancreatitis. Caution is recommended in patients with a history of pancreatitis or alcohol abuse. Patients with severe or very severe (grade 3 or greater) hypertriglyceridemia should be appropriately managed to reduce the risk of pancreatitis.

Inform patients of the possibility of developing pancreatitis that may be accompanied by nausea, vomiting, abdominal pain, or abdominal discomfort, and to promptly report these symptoms.

Immune

Hepatitis B Virus Reactivation

Reactivation of hepatitis B virus (HBV) has occurred in patients who are chronic carriers of this virus after receiving BCR-ABL tyrosine kinase inhibitors. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or death.

Patients currently receiving ICLUSIG should be tested for HBV infection, if clinically indicated, in order to identify chronic carriers of the virus. Patients should be tested for HBV infection before initiating treatment with ICLUSIG. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with ICLUSIG should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

Metabolism

Tumour Lysis Syndrome

Serious tumour lysis syndrome occurred in 2 patients (<1%) in PACE. One case occurred in an AP-CML patient and one case occurred in a BP-CML patient. Hyperuricemia occurred in 32 patients (7%), most of whom were CP-CML patients (19 patients).

In OPTIC, serious tumour lysis syndrome occurred in 1 patient (1%) in the 45 mg cohort). Hyperuricemia occurred in 2% of patients.

Ensure adequate hydration and high uric acid levels should be corrected prior to initiating therapy with ICLUSIG.

Monitoring and Laboratory Tests

ICLUSIG is associated with serious events of arterial occlusion, cardiac arrhythmias and cardiac failure. Before starting treatment with ICLUSIG, the cardiovascular status of the patient should be assessed and cardiovascular risk factors should be actively managed (see 9.4 Drug-Drug Interactions). Cardiovascular status should continue to be monitored and therapy optimized during treatment with ICLUSIG (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 4.2 Recommended Dose and Dosage Adjustment).

Hypertension may contribute to risk of arterial occlusive events (AOEs). During ICLUSIG treatment, blood pressure should be monitored and managed to avoid hypertension (see 7 WARNINGS AND PRECAUTIONS, Hypertension).

ICLUSIG is associated with severe (grade 3 or greater) thrombocytopenia, neutropenia, and anemia. A complete blood count should be performed every 2 weeks for the first 3 months and then monthly or as clinically indicated (see 7 WARNINGS AND PRECAUTIONS, Myelosuppression and 4.2 Recommended Dose and Dosage Adjustment).

ICLUSIG may result in elevation in ALT, AST, bilirubin, and alkaline phosphatase. Liver function tests should be performed at baseline and periodically, as clinically indicated (see 7 WARNINGS AND PRECAUTIONS, Hepatotoxicity and 4.2 Recommended Dose and Dosage Adjustment).

ICLUSIG is associated with pancreatitis. Check serum amylase/lipase every 2 weeks for the first 2 months and then periodically thereafter. Dose interruption or reduction may be required (see **Error! Reference source not found.**). If lipase elevations are accompanied by abdominal symptoms, ICLUSIG should be withheld and patients evaluated for evidence of pancreatitis (see 4.2 Recommended Dose

and Dosage Adjustment and 7 WARNINGS AND PRECAUTIONS, Pancreatitis and Serum Lipase).

Left ventricular ejection fraction (LVEF) should be evaluated in all patients prior to initiation of treatment with ICLUSIG, at three months after initiation of ICLUSIG and whenever clinically indicated (see 7 WARNINGS AND PRECAUTIONS, Heart Failure and Left Ventricular Dysfunction).

Monitor for evidence of venous thromboembolic events (VTEs). Interrupt treatment with ICLUSIG or consider discontinuation in patients who develop venous thromboembolism (see 7 WARNINGS AND PRECAUTIONS, Venous Thromboembolic Events and 4.2 Recommended Dose and Dosage Adjustment).

Serious ocular toxicities leading to blindness or blurred vision occurred in ICLUSIG-treated patients. Conduct comprehensive eye exams at baseline and periodically during treatment (see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic).

Ensure adequate hydration and correct uric acid levels prior to initiating therapy with ICLUSIG if tumour lysis syndrome is considered a substantial risk (see 7 WARNINGS AND PRECAUTIONS, Tumour Lysis Syndrome).

Patients should be weighed and monitored regularly for signs and symptoms of fluid retention (see 7 WARNINGS AND PRECAUTIONS, Fluid Retention).

Phosphate should be measured at baseline and monitored during ICLUSIG treatment, as clinically indicated.

Neurologic

Peripheral and cranial neuropathies occurred in ICLUSIG-treated patients. Overall, 20% (88/449) of ICLUSIG-treated patients in the PACE trial experienced a peripheral neuropathy event of any grade (2%, grade 3/4). The most common peripheral neuropathies reported were paresthesia (5%, 24/449), peripheral neuropathy (5%, 20/449), hypoesthesia (4%, 16/449), muscular weakness (2%, 10/449), dysgeusia (1%, 6/449), and hyperesthesia (1%, 5/449). Cranial neuropathy developed in 3% (13/449) of ICLUSIG-treated patients (<1%, 3/449 - grade 3/4). Cases of ataxia and convulsion were also reported. Of the patients who developed peripheral neuropathy, 22% (19/88) developed neuropathy during the first month of treatment.

Of the patients who received a starting dose of 45 mg in OPTIC, 6% (6/94) experienced a peripheral neuropathy event (none grade 3/4). Paraesthesia, hypoesthesia, and muscular weakness were experienced in 2 patients each (2%) and peripheral neuropathy in one patient (1%). Cranial neuropathy events were reported in 2 patients.

Inform patients of the possibility of developing peripheral or cranial neuropathy while being treated with ICLUSIG. Advise patients to report symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness.

Ophthalmologic

Serious ocular toxicities leading to blindness or blurred vision occurred in ICLUSIG-treated patients.

In PACE, ocular toxicities occurred in 30% (136/449) of patients. The most common (≥2%) ocular toxicities were dry eye (8%), blurred vision (6%), eye pain (4%), cataract (3%), and periorbital edema (2%). The following retinal toxicities occurred in 1% of patients for each: eye hemorrhage, macular edema, retinal vein occlusion, retinal hemorrhage, and vitreous floaters (see 8 ADVERSE REACTIONS). A case of retinal artery occlusion (grade 4) while taking a 45 mg dose of ICLUSIG was reported.

Of the 94 patients who received a starting dose of 45 mg in OPTIC, ocular toxicities occurred in 11% of patients. The most common (≥2%) were blurred vision and eye pain. Retinal toxicities, including age-related macular degeneration and retinal vein occlusion, occurred in one patient each.

Conduct comprehensive eye exams at baseline and periodically during treatment. ICLUSIG should be interrupted if an AOE is suspected. Patients should be monitored for the occurrence of vision problems (see 7 WARNINGS AND PRECAUTIONS, Arterial Occlusive Events).

Inform patients of the possibility of ocular toxicity while being treated with ICLUSIG. Advise patients to report symptoms of ocular toxicity, such as blurred vision, dry eye, or eye pain.

Posterior Reversible Encephalopathy Syndrome (PRES)

Post-marketing cases of Posterior Reversible Encephalopathy Syndrome (PRES, also known as Reversible Posterior Leukoencephalopathy Syndrome – RPLS) have been reported in ICLUSIG-treated patients (see 8.5 Post-Market Adverse Reactions). PRES is a serious neurological disorder that can present with signs and symptoms such as seizure with hemiplegia, headache, decreased alertness, altered mental functioning, vision loss, and other visual and neurological disturbances. Hypertension is often present and diagnosis is made with supportive findings on Magnetic Resonance Imaging (MRI) of the brain.

If PRES is diagnosed during treatment, interrupt ICLUSIG treatment and resume treatment only once the event is resolved and if the benefit of continued treatment outweighs the risk of PRES.

Reproductive Health: Female and Male Potential

- **Fertility**

Ponatinib may impair female fertility. The effect of ponatinib on male and female fertility in humans is unknown. No human data on the effect of ponatinib on fertility are available. In rats, treatment with ponatinib has shown impairment of female fertility. Male fertility was not affected by ponatinib treatment. The clinical relevance of these findings to human fertility is unknown (see 16 NON-CLINICAL TOXICOLOGY).

- **Teratogenic Risk**

Ponatinib may cause fetal harm when administered to pregnant women. There are no clinical data from the use of ponatinib in pregnant women. Studies in animals have shown teratogenic and embryo-fetal toxic effects at exposures lower than human exposures at the recommended human dose (see 16 NON-CLINICAL TOXICOLOGY). Women of childbearing age being treated with ICLUSIG should be advised of the potential risk to a fetus, and advised not to become pregnant (see 7.1.1 Pregnant Women and 7.1.5 Men and Women with Childbearing Potential). Men being treated with ICLUSIG should be advised not to father a child during treatment. An effective method of contraception should be used during treatment. It is unknown whether ICLUSIG affects the effectiveness of systemic hormonal contraceptives. An alternative or additional method of contraception should be used.

7.1 Special Populations

7.1.1 Pregnant Women

Ponatinib may cause fetal harm when administered to pregnant women. Embryo-fetal toxicity and teratogenicity have been reported in animal studies at exposures lower than human exposures at the recommended human dose (see 16 NON-CLINICAL TOXICOLOGY). There are no data regarding the use

of ICLUSIG in pregnant women. The potential risk for humans is unknown. Patients must be informed of the potential risk to the fetus.

Inform patients that ICLUSIG can cause fetal harm when administered to a pregnant woman. Advise women of the potential hazard to a fetus and to avoid becoming pregnant during the treatment of ICLUSIG.

7.1.2 Breast-feeding

It is unknown if ponatinib is excreted in human milk. Breast-feeding should be stopped during treatment with ICLUSIG.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of ICLUSIG in patients less than 18 years of age have not been established. No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Compared to patients < 65 years of age, older patients (≥ 65 years of age) are more likely to experience reduced efficacy and adverse reactions. Of the 449 patients in the clinical study of ICLUSIG, 155 (35%) were ≥ 65 years of age. CP-CML patients ≥ 65 years of age had a lower MCyR rate, 40%, compared with patients between 45 and 64 years of age (MCyR 61%) and patients between 18 and 44 years of age (MCyR 72%). Patients ≥ 65 years of age are more likely to experience adverse reactions, including vascular occlusion, decreased platelet count, peripheral edema, increased lipase, dyspnea, asthenia, muscle spasms, and decreased appetite.

In general, dose selection for an older patient should be done cautiously, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, of concomitant disease or other drug therapy.

7.1.5 Men and Women with Childbearing Potential

Women of childbearing age being treated with ICLUSIG should be advised not to become pregnant and men being treated with ICLUSIG should be advised not to father a child during treatment. An effective method of birth control should be used during ICLUSIG treatment. It is unknown whether ICLUSIG affects the effectiveness of systemic hormonal contraceptives. An alternative or additional method of contraception should be used. See 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential, Fertility.

7.1.6 Lactose Intolerance

ICLUSIG contains 121 mg of lactose monohydrate in a 45 mg daily dose. Advise patients who have or may have an intolerance to lactose. Patients with rare hereditary disorders of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take ICLUSIG (see 2 CONTRAINDICATIONS).

7.1.7 Hepatic Impairment

Administer ICLUSIG at a starting dose of 30 mg once daily in patients with hepatic impairment (Child Pugh A, B or C) (see 4.2 Recommended Dose and Dosage Adjustment). Hepatic elimination is a major route of excretion for ICLUSIG.

A single dose of ICLUSIG 30 mg was administered to patients with mild, moderate, and severe hepatic impairment (Child-Pugh Classes A, B, and C, respectively) and to healthy subjects. Overall, no major differences in ponatinib pharmacokinetics were observed in patients with varying degrees of hepatic impairment as compared to healthy subjects. However, there was an increased overall incidence of adverse reactions in patients with severe hepatic impairment, including a case of severe pancreatitis. The safety of multiple ICLUSIG doses, or doses higher than 30 mg, has not been studied in patients with hepatic impairment. Caution is recommended when administering ICLUSIG to patients with hepatic impairment.

7.1.8 Renal Impairment

ICLUSIG has not been studied in patients with severe renal impairment (creatinine clearance <30 mL/min). Caution is recommended when administering ICLUSIG to patients with severe renal impairment or end-stage renal disease.

Mild to moderate renal impairment (creatinine clearance 30 to 89 mL/min) did not have a clinically meaningful effect on the pharmacokinetics of ponatinib based on a population pharmacokinetic analysis.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Previously Treated CML or Ph+ ALL

Study AP24534-10-201 (PACE) is a multicenter trial in 449 adult patients with CML (CP-CML, AP-CML or BP-CML) or Ph+ ALL patients who were resistant or intolerant to prior TKI therapy including those with a BCR-ABL T315I mutation. All patients received a starting dose of 45 mg ICLUSIG once daily. The median duration of treatment with ICLUSIG was 32.2 months in CP-CML patients, 19.4 months in AP-CML patients, and 2.8 months in BP-CML/Ph+ ALL patients. The rates of treatment-emergent adverse events resulting in discontinuation were 21% (57/270) in CP-CML, 12% (10/85) in AP-CML, 15% (9/62) in BP-CML, and 9% (3/32) in Ph+ ALL.

The most common non-hematologic adverse events (≥ 20%) in previously treated CML or Ph+ ALL patients (PACE) who received ICLUSIG at a starting dose of 45 mg once daily were abdominal pain (43%), rash (42%), constipation (38%), headache (38%), dry skin (37%), hypertension (32%), fatigue (31%), arthralgia (30%), pyrexia (30%), nausea (30%), diarrhea (22%), lipase increased (22%), vomiting (22%), myalgia (21%), pain in extremity (21%), and back pain (20%). The most common adverse events (≥ 1%) that led to treatment discontinuation was platelet count decreased (4%). The most common adverse events (≥ 5%) that led to dose modification (interruption or dose reduction) were platelet count decreased (31%), neutrophil count decreased (14%), lipase increased (13%), arterial occlusive events (13%), abdominal pain (13%), rash (9%), anemia (7%), pancreatitis (6%), ALT increased (6%), AST increased (5%), and hypertension (5%).

Previously Treated CP-CML

Study AP24534-14-203 (OPTIC) is a multicenter trial in 282 adult patients with resistant CP-CML who received at least 2 prior TKI therapies and had demonstrated resistance to treatment or had the T315I mutation. Patients were randomized 1:1:1 to receive 1 of 3 starting doses of ICLUSIG once daily: 45 mg, 30 mg, or 15 mg. The median duration of ICLUSIG treatment in the 45 mg cohort was 21 months. Patients who received a starting dose of 45 mg had a mandatory dose reduction to 15 mg once daily upon achievement of ≤1% BCR-ABL1^{IS}.

The most common non-hematologic adverse events (≥ 10%) in the 45 mg cohort (n=94) were hypertension, ALT increased, lipase increased, headache, pyrexia, hypertriglyceridemia, AST increased, rash, dry skin, constipation, abdominal pain/abdominal pain upper, and arthralgia. The most common adverse events (≥ 2%) that led to treatment discontinuation was platelet count decreased (3.2%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Previously Treated CML or Ph+ ALL

The most common adverse drug reactions (≥ 5%) are presented in Table 4. Overall, the very common adverse reactions (≥ 10%) were platelet count decreased, rash, constipation, headache, dry skin, abdominal pain, fatigue, hypertension, arthralgia, nausea, neutrophil count decreased, anemia, lipase increased, myalgia, ALT increased, AST increased. The most common serious adverse drug reactions reported were pancreatitis and peripheral arterial occlusive disease (Table 5).

Table 4. Most Common Adverse Drug Reactions Occurring in ≥ 5% of Resistant or Intolerant CP-CML, AP-CML, BP-CML and Ph+ ALL Patients* in Phase 2 Study AP24534-10-201 (PACE, N=449)

System Organ Class Preferred Term	CP-CML (N=270)		AP-CML (N=85)		BP-CML (N=62)		Ph+ ALL (N=32)	
	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)
Blood and lymphatic system disorders								
Neutropenia	16	13	27	27	18	15	9	9
Anemia	12	6	21	14	23	21	16	13
Febrile neutropenia	<1	<1	2	2	3	3	6	6
Cardiac disorders								
Cardiac failure**	5	4	6	5	7	5	0	0
Angina pectoris	6	1	0	0	2	0	0	0
Eye disorders								
Dry eye	6	1	5	0	2	0	3	0
Gastrointestinal disorders								
Abdominal pain	29	7	18	5	10	2	19	6
Constipation	21	2	14	1	5	0	19	3
Nausea	16	0	12	0	21	0	3	0
Vomiting	8	1	8	0	13	0	3	0
Diarrhea	9	<1	11	0	2	0	3	3
Pancreatitis	7	7	8	6	5	3	0	0
Abdominal distension	6	0	4	0	5	0	0	0
Dry mouth	6	0	1	0	2	0	3	0
General disorders and administration site conditions								
Fatigue	21	2	21	1	11	3	9	0
Asthenia	10	1	6	1	8	2	0	0
Pyrexia	9	0	8	1	3	0	13	0
Pain	7	1	7	0	7	2	0	0
Edema peripheral	6	0	7	0	5	0	9	0
Infections and infestations								
Folliculitis	4	0	4	0	2	0	6	0
Investigations								
Platelet count decreased	42	32	45	35	27	26	9	6
Lipase increased	26	12	15	13	13	11	9	6
Neutrophil count decreased	17	15	29	29	23	18	13	13

System Organ Class Preferred Term	CP-CML (N=270)		AP-CML (N=85)		BP-CML (N=62)		Ph+ ALL (N=32)	
	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)
Alanine aminotransferase increased	15	4	17	2	10	3	6	3
Aspartate aminotransferase increased	12	3	14	4	8	2	6	3
Amylase increased	7	3	7	4	5	3	3	0
Gamma-glutamyltransferase increased	6	3	9	4	3	3	0	0
Blood alkaline phosphatase increased	6	<1	11	1	3	0	0	0
Weight decreased	5	0	4	0	2	0	3	0
White blood cell count decreased	4	3	11	7	0	0	3	3
Metabolism and nutrition disorders								
Decreased appetite	7	<1	7	1	5	0	9	0
Dehydration	2	<1	1	1	0	0	6	3
Musculoskeletal and connective tissue disorders								
Arthralgia	19	2	20	2	13	0	3	0
Myalgia	19	1	20	0	13	0	6	0
Pain in extremity	13	2	7	0	5	0	0	0
Muscle spasms	11	0	4	0	2	0	6	0
Bone pain	10	<1	6	0	3	0	0	0
Back pain	9	1	2	0	0	0	0	0
Musculoskeletal pain	6	1	4	0	2	0	0	0
Nervous system disorders								
Headache	26	3	13	0	11	2	13	0
Dizziness	7	<1	2	0	0	0	0	0
Reproductive system and breast disorders								
Erectile dysfunction	4	0	6	0	0	0	0	0
Psychiatric disorders								
Confusional state	1	<1	0	0	0	0	6	0
Disorientation	<1	0	0	0	0	0	6	0
Respiratory, thoracic and mediastinal disorders								

System Organ Class Preferred Term	CP-CML (N=270)		AP-CML (N=85)		BP-CML (N=62)		Ph+ ALL (N=32)	
	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)
Dyspnea	8	2	8	0	7	2	0	0
Pleural effusion	3	1	7	1	5	0	9	0
Skin and subcutaneous tissue disorders								
Rash	42	4	34	4	24	3	19	3
Dry skin	41	3	25	1	18	2	22	0
Erythema	9	1	7	0	5	0	6	0
Rash pruritic	9	0	11	2	2	0	3	0
Pruritus	10	<1	4	0	2	2	0	0
Alopecia	7	0	7	0	5	0	6	0
Skin exfoliation	7	0	2	0	2	0	0	0
Exfoliative rash	3	0	7	0	2	0	0	0
Vascular disorders								
Hypertension	23	7	14	6	3	3	3	3
Deep vein thrombosis	<1	0	0	0	0	0	6	3

Treatment related adverse events as assessed by the investigator. The incidence rates reported in 7 WARNINGS AND PRECAUTIONS section are treatment-emergent frequencies.
* All patients received a starting dose of 45 mg ICLUSIG once daily.
**Cardiac failure includes the following MedDRA preferred terms: cardiac failure, cardiac failure congestive, cardiac failure acute, cardiac failure chronic, left ventricular dysfunction, ejection fraction decreased.
MedDRA Version 19.0 was used for coding adverse events.

Other Common (≥ 1% and < 5%) clinical trial adverse drug reactions include:

- Blood and lymphatic system disorders: pancytopenia
- Cardiac disorders: acute coronary syndrome, acute myocardial infarction/ myocardial infarction, atrial fibrillation, coronary artery disease, palpitations, pericardial effusion
- Eye disorders: vision blurred
- Gastrointestinal disorders: abdominal discomfort, dry mouth, dyspepsia, gastroesophageal reflux disease, gastrointestinal hemorrhage (includes fatal events), gingival bleeding, mouth ulceration, stomatitis
- General disorders and administration site conditions: chest pain, chills, influenza like illness, malaise, non-cardiac chest pain, peripheral swelling
- Infections and infestations: cellulitis, conjunctivitis, pneumonia, upper respiratory tract infection
- Investigations: blood bilirubin increased, blood cholesterol increased, blood creatinine increased, lymphocyte count decreased
- Metabolism and nutrition disorders: hyperglycemia, hypertriglyceridemia, hyperuricemia, hypocalcemia, hypokalemia, hyponatremia, hypophosphatemia
- Musculoskeletal and connective tissue disorders: musculoskeletal chest pain, neck pain
- Nervous system disorders: cerebral infarction, cerebrovascular accident, hypoesthesia, lethargy, migraine, neuropathy peripheral, paresthesia
- Psychiatric disorders: insomnia

- Respiratory, thoracic and mediastinal disorders: cough, dysphonia, epistaxis, pulmonary hypertension
- Skin and subcutaneous tissue disorders: dermatitis exfoliative, ecchymosis, hyperhidrosis, hyperkeratosis, night sweats, pain of skin, petechiae, skin hyperpigmentation
- Vascular disorders: flushing, hot flush, intermittent claudication, peripheral arterial occlusive disease, peripheral artery stenosis, peripheral artery occlusion

Table 5. Serious Adverse Drug Reactions Occurring in ≥ 1% of Resistant or Intolerant CP-CML, AP-CML, BP-CML and Ph+ ALL Patients* in Phase 2 Study AP24534-10-201 (PACE, N=449)

MedDRA System Organ Class Preferred Term	**N (%)**
Blood and lymphatic system disorders	
Anemia	6 (1.3%)
Febrile neutropenia	5 (1.1%)
Pancytopenia	5 (1.1%)
Cardiac disorders	
Arterial occlusive events	62 (13.8%)
Cardiac vascular	31 (6.9%)
Angina pectoris	12 (2.7%)
Acute myocardial infarction/myocardial infarction[a]	9 (2.0%)
Coronary artery disease	8 (1.8%)
Acute coronary syndrome	6 (1.3%)
Cerebrovascular	20 (4.5%)
Cerebral infarction	7 (1.6%)
Cerebrovascular accident	5 (1.1%)
Peripheral vascular	27 (6.0%)
Peripheral arterial occlusive disease	14 (3.1%)
Peripheral artery stenosis	6 (1.3%)
Venous thromboembolic events[b]	9 (2.0%)
Atrial fibrillation	10 (2.2%)
Cardiac failure congestive	7 (1.6%)
Pericardial effusion	6 (1.3%)
Gastrointestinal disorders	
Pancreatitis	25 (5.6%)
Abdominal pain	9 (2.0%)
General disorders and administration site conditions	
Pyrexia	5 (1.1%)
Investigations	
Lipase increased	9 (2.0%)
Platelet count decreased	8 (1.8%)
Neutrophil count decreased	5 (1.1%)
Vascular disorders	
Hypertension	8 (1.8%)

[a] Includes fatal events.

[b] Individual venous thromboembolic events occurred at a frequency of < 1%.

* All patients received a starting dose of 45 mg ICLUSIG once daily.

MedDRA Version 19.0 was used for coding adverse events.

Previously Treated CP-CML

Adverse reactions reported in CP-CML patients from OPTIC were generally similar to those reported for CP-CML patients from PACE.

Common adverse drug reactions (≥ 5%) in the 45 mg cohort are presented in Table 6. Grade 3/4 adverse drug reactions (≥ 5%) were thrombocytopenia (30%), neutropenia (18%), anemia (10%), lipase increased (10%), and platelet count decreased (5%). In the 45 mg cohort, serious adverse drug reactions (≥ 2%) were thrombocytopenia (4%), pyrexia (3%), sudden death (2%), neutropenia (2%), anemia (2%), and atrial fibrillation (2%).

Table 6. Common Adverse Drug Reactions Occurring in ≥ 5% of Previously Treated CP-CML Patients who Received ICLUSIG at Starting Dose of 45 mg followed by Reduction to 15 mg after Achievement of ≤ 1% BCR-ABL1^{IS} in Phase 2 Study AP24534-14-203 (OPTIC, N=282)

System Organ Class Preferred Term	CP-CML (N=94)	
	Any Grade (%)	**Grade 3/4 (%)**
Blood and lymphatic system disorders		
Thrombocytopenia	42	30
Neutropenia	30	18
Anemia	18	10
Leukopenia	5	2
Gastrointestinal disorders		
Constipation	5	0
General disorders and administration site conditions		
Pyrexia	6	1
Fatigue	5	1
Infections and infestations		
Folliculitis	5	0
Metabolism and nutrition disorders		
Hypertriglyceridemia	13	0
Musculoskeletal and connective tissue disorders		
Myalgia	5	1
Nervous system disorders		
Headache	9	0
Investigations		
Lipase increased	19	10
Alanine aminotransferase increased	16	3
Platelet count decreased	12	5
Aspartate aminotransferase increased	10	0
Blood alkaline phosphatase increased	5	2
Skin and subcutaneous tissue disorders		

System Organ Class Preferred Term	CP-CML (N=94)	
	Any Grade (%)	Grade 3/4 (%)
Rash	12	0
Dermatitis	6	1
Dry skin	6	0
Rash maculo-papular	5	1
Vascular disorders		
Hypertension	18	4

Treatment related adverse events as assessed by the investigator. The incidence rates reported in 7 WARNINGS AND PRECAUTIONS section are treatment-emergent frequencies.
MedDRA Version 23.0 was used for coding adverse events.

8.3 Less Common Clinical Trial Adverse Reactions

Previously Treated CML or Ph+ ALL

Less common (< 1%) clinical trial adverse drug reactions include the following:

- Cardiac disorder: atrial flutter, bradycardia, cardiac discomfort, coronary artery occlusion, ischemic cardiomyopathy, myocardial ischemia, sinus bradycardia, tachycardia, ventricular tachycardia
- Ear and labyrinth disorders: tinnitus, vertigo
- Endocrine disorders: hypothyroidism
- Eye disorders: blepharitis, cataract, conjunctival hemorrhage, conjunctival hyperemia, eyelid edema, eye pain, eye swelling, ocular hyperemia, periorbital edema, retinal artery occlusion, retinal vein thrombosis and occlusion, and visual impairment
- Gastrointestinal disorders: ascites, flatulence, GI hemorrhage/upper GI hemorrhage, gingival bleeding, hemorrhoidal hemorrhage, mouth ulceration
- General disorders and administration site conditions: face edema, localised edema
- Hepatobiliary disorders: hepatic failure, hepatocellular injury, hepatotoxicity, jaundice
- Infections and infestations: herpes zoster, sepsis/septic shock, urinary tract infection
- Injury, poisoning and procedural complications: contusion
- Investigations: blood lactate dehydrogenase increased, blood uric acid increased, electrocardiogram QT prolonged, transaminases increased, weight increased
- Metabolism and nutrition disorders: diabetes mellitus, fluid retention, gout, hyperlipidemia, hypoalbuminemia, tumour lysis syndrome
- Musculoskeletal and connective tissue disorders: flank pain, musculoskeletal stiffness, upper extremity mass
- Neoplasms benign, malignant unspecified (incl cysts and polyps): melanocytic nevus
- Nervous system disorders: amnesia, burning sensation, carotid artery stenosis, cerebral artery stenosis, cerebral hemorrhage, cerebral ischemia, dysgeusia, hyperesthesia, peripheral sensory neuropathy, syncope, transient ischemic attack, tremor
- Psychiatric disorders: anxiety, depression
- Renal and urinary disorders: acute kidney injury, renal artery stenosis
- Respiratory, thoracic and mediastinal disorders: dry throat, pulmonary embolism (includes fatal events)

- Skin and subcutaneous tissue disorders: acne, actinic keratosis, dermatitis acneiform, dermatitis psoriasiform, erythema multiforme, generalised erythema, ichthyosis acquired, keratosis pilaris, skin discoloration, skin lesion, toxic skin eruption
- Vascular disorders: embolism venous, hematoma, hypertensive crisis, peripheral ischemia, peripheral vascular disorder, poor peripheral circulation, splenic infarction

Previously Treated CP-CML

Less common (< 1%) clinical trial adverse drug reactions reported in CP-CML patients from OPTIC were generally similar to those reported for CP-CML patients from PACE.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Previously Treated CML or Ph+ ALL

In PACE, myelosuppression was commonly reported in all patient populations of resistant or intolerant CML and Ph+ ALL. The frequency of grade 3 or 4 thrombocytopenia, neutropenia, and anemia was higher in patients with AP-CML and BP-CML/Ph+ ALL than in patients with CP-CML (see Table 7). Myelosuppression was reported in patients with normal baseline laboratory values as well as in patients with pre-existing laboratory abnormalities.

Table 7. Incidence of Laboratory Abnormalities in ≥ 20% of Resistant or Intolerant CML and Ph+ ALL Patients from Study AP24534-10-201 (PACE, N=449)

Laboratory Test	CP-CML (N=270)		AP-CML (N=85)		BP-CML (N=62)		Ph+ ALL (N=32)	
	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)
Hematology								
Thrombocytopenia (platelet count decreased)	62	35	79	49	50	45	50	47
Neutropenia (ANC decreased)	46	23	80	52	60	48	69	59
Leukopenia (WBC decreased)	46	12	78	37	65	48	72	63
Lymphopenia	44	10	61	25	60	32	66	19
Anemia (Hgb decreased)	43	8	65	31	61	52	75	34
Biochemistry								
Glucose increased	56	8	58	13	44	2	44	0
Lipase increased	46	13	35	13	23	15	19	13
ALT increased	43	4	47	8	34	8	22	6
AST increased	38	3	31	5	34	5	16	0
Phosphorus decreased	37	10	42	13	21	11	9	3

Laboratory Test	CP-CML (N=270)		AP-CML (N=85)		BP-CML (N=62)		Ph+ ALL (N=32)	
	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)
Alkaline phosphatase increased	37	2	44	4	47	3	38	0
Albumin decreased	28	<1	32	0	29	0	19	0
Sodium decreased	27	6	34	6	27	2	13	3
Calcium decreased	26	<1	35	2	42	2	31	0
Creatinine increased	23	<1	26	0	19	0	3	0
Potassium increased	22	2	19	1	15	5	16	0
Bicarbonate decreased	20	<1	25	0	16	0	13	0

Previously Treated CP-CML

Table 8. Incidence of Laboratory Abnormalities from Baseline in ≥ 20% of CP-CML Patients from Study AP24534-14-203 (OPTIC, N=282)

Laboratory Test	45 mg Cohort (N=94)	
	Any Grade (%)	Grade 3/4 (%)
Hematology		
Platelet count decreased	65	31
White blood cell decreased	54	13
Neutrophil count decreased	32	22
Hemoglobin decreased	32	14
Lymphocytes decreased	18	7
Biochemistry		
ALT increased	49	1
Glucose increased	45	1
Hypertriglyceridemia	44	3
AST Increased	40	0
Cholesterol High	35	1
Lipase increased	34	12
Hypophosphatemia	27	3
Direct bilirubin increased	23	2
Alkaline Phosphatase Increased	23	1

Electrocardiogram Findings

In a phase 3 randomised, open-label study of ICLUSIG versus active comparator in adult patients with newly diagnosed CP-CML patients, the ICLUSIG group received once daily oral administration of 45 mg for 28 day continuous cycles, with dose adjustments based on tolerability. At the month 3 assessment, ICLUSIG was associated with statistically significant decreases from baseline in the QTcF interval and heart rate. The mean change from baseline in the QTcF interval (N=78) was -8.2 ms (90% CI -11.98, -4.88) and the mean change from baseline in heart rate (N=84) was -5.6 bpm (90% CI -7.81, -3.43).

8.5 Post-Market Adverse Reactions

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The safety profile observed in post-marketing is similar to that observed during clinical studies. However, serious cases of Posterior Reversible Encephalopathy Syndrome (PRES, also known as Reversible Posterior Leukoencephalopathy Syndrome – RPLS) occurred in patients receiving ICLUSIG. Blurred vision or bilateral blindness was reported in some patients after 5 days of treatment. Hepatitis B virus reactivation has been reported in patients who are chronic carriers of this virus after receiving BCR-ABL tyrosine kinase inhibitors.

In addition, the following adverse reactions have been identified during post-marketing use of ICLUSIG: urinary tract infection, chest pain, dehydration, peripheral swelling, panniculitis, squamous cell carcinoma, and severe cutaneous reaction (e.g., Erythema multiforme, Stevens-Johnson Syndrome).

Artery dissection and artery aneurysm (including rupture) have been reported in association with VEGFR TKIs, including ICLUSIG.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Ponatinib is metabolized by esterases and/or amidases, and also by CYP3A4. Avoid co-administration of ICLUSIG with strong CYP3A inhibitors and strong CYP3A inducers.

In vitro studies indicate that drug-drug interactions are unlikely to occur as a result of ponatinib-mediated inhibition of the metabolism of substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A or CYP2D6. An *in vitro* study in human hepatocytes indicated that drug-drug interactions are also unlikely to occur as a result of ponatinib-mediated induction of the metabolism of substrates for CYP1A2, CYP2B6, or CYP3A.

At therapeutic plasma concentrations, ponatinib did not inhibit OATP1B1 or OATP1B3, OCT1 or OCT2, organic anion transporters OAT1 or OAT3, or bile salt export pump (BSEP) *in vitro*. Clinical drug-drug interactions are unlikely to occur as a result of ponatinib-mediated inhibition of these transporter substrates. *In vitro*, ponatinib is an inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Ponatinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp or BCRP and may increase their therapeutic effect and adverse reactions. Close clinical surveillance is recommended when ponatinib is co-administered with P-gp and BCRP substrates.

See 9.4 Drug-Drug Interactions.

9.3 Drug-Behavioural Interactions

No studies have been conducted on the potential interaction between ICLUSIG and alcohol consumption.

9.4 Drug-Drug Interactions

Substances that increase ponatinib plasma concentrations

CYP3A inhibitors

Ponatinib is primarily metabolized by CYP3A4. Therefore, concomitant use of substances which inhibit CYP3A may increase ponatinib plasma concentrations.

Co-administration in healthy volunteers of a single 15 mg oral dose of ICLUSIG in the presence of ketoconazole (400 mg daily), a strong CYP3A inhibitor, resulted in increases in ponatinib systemic exposure, with ponatinib $AUC_{0-\infty}$ and C_{max} values that were 78% and 47% higher, respectively, than those seen when ponatinib was administered alone. Patients being co-administered ICLUSIG with strong CYP3A inhibitors may be at increased risk for adverse reactions.

Avoid co-administration of ICLUSIG with strong CYP3A inhibitors such as clarithromycin, itraconazole, ketoconazole, nelfinavir, ritonavir, voriconazole, posaconazole, and grapefruit juice. If co-administration of a strong CYP3A inhibitor cannot be avoided, reduce the ICLUSIG dosage as recommended in Table 9. After the strong CYP3A inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the ICLUSIG dosage that was tolerated prior to initiating the strong CYP3A inhibitor.

Table 9. Recommended ICLUSIG Dosage for Co-administration with Strong CYP3A Inhibitors

Current ICLUSIG Dosage	Recommended ICLUSIG Dosage with a Strong CYP3A Inhibitor
45 mg orally once daily	30 mg orally once daily
30 mg orally once daily	15 mg orally once daily
15 mg orally once daily	Discontinue ICLUSIG.

Substances that decrease ponatinib plasma concentrations

CYP3A inducers

Ponatinib is primarily metabolized by CYP3A4. Therefore, concomitant use of CYP3A inducers may decrease ponatinib plasma concentrations. Co-administration of ICLUSIG with strong CYP3A inducers (such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, and St. John's Wort) should be avoided unless the benefit outweighs the possible risk of decreased ponatinib exposure. Monitor patients for signs of reduced efficacy. Selection of concomitant medications with no or minimal CYP3A induction potential is recommended.

Co-administration in healthy volunteers of a single 45 mg dose of ICLUSIG in the presence of rifampicin (600 mg daily for 9 days), a strong CYP3A inducer, resulted in decreases in ponatinib systemic exposure, with ponatinib $AUC_{0-\infty}$ and C_{max} values that were 62% and 42% lower, respectively, than those seen when ponatinib was administered alone.

Gastric pH Elevating Drugs

The aqueous solubility of ponatinib is pH-dependent, with higher pH resulting in lower solubility.

Administration of a single 45 mg dose of ICLUSIG following multiple doses of a potent inhibitor of a proton pump inhibitor, lansoprazole, 60 mg QD for 2 days, in 18 healthy volunteers, resulted in reductions in ponatinib C_{max} by 25% without a change in overall systemic exposure ($AUC_{0-\infty}$), respective to those seen when ICLUSIG was administered alone. Median T_{max} was increased by 1 hour when ICLUSIG was administered following lansoprazole pretreatment.

ICLUSIG may be administered concurrently with proton pump inhibitors or other drugs that raise gastric pH without the need for adjustment of the ICLUSIG dose or separation of administration.

Substances that may have their plasma concentrations altered by ponatinib

Transporter substrates

In vitro, ponatinib is an inhibitor of P-gp and BCRP. Therefore, ponatinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp (e.g., digoxin, dabigatran, colchicine, pravastatin) or BCRP (e.g., methotrexate, rosuvastatin, sulfasalazine) and may increase their therapeutic effect and adverse reactions. Close clinical surveillance is recommended when ICLUSIG is co-administered with P-gp or BCRP substrates.

9.5 Drug-Food Interactions

Administration of ICLUSIG with a high- or low-fat meal, or without food, does not change the pharmacokinetics of ponatinib (see 10.3 Pharmacokinetics).

Products and juices containing grapefruit, star fruit, pomegranate, Seville oranges and other similar fruits that are known to inhibit CYP3A should be avoided at any time.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been studied. St. John's Wort is a potent CYP3A inducer. Co-administration of St. John's Wort with ICLUSIG may lead to increased ponatinib metabolism and therefore decreased ponatinib plasma concentrations (see 9.4 Drug-Drug Interactions).

Co-administration of St. John's Wort with ICLUSIG should be avoided.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been studied.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Ponatinib is a kinase inhibitor. Ponatinib is a potent pan-breakpoint cluster region-Abelson 1 (BCR-ABL) inhibitor with structural elements, including a carbon-carbon triple-bond that enables high affinity binding to native BCR-ABL and mutant forms of the ABL kinase. Ponatinib inhibits the *in vitro* tyrosine kinase activity of ABL and T315I mutant ABL with IC_{50}s values of 0.4 and 2.0 nM, respectively. Ponatinib inhibits the *in vitro* activity of additional kinases with IC_{50}s between 0.1 and 20 nM, including members of the VEGFR, PDGFR, FGFR, EPH receptors and SRC families of kinases, and KIT, RET, TIE2, and FLT3.

10.2 Pharmacodynamics

In cellular assays, ponatinib was able to overcome imatinib, dasatinib, and nilotinib resistance mediated by BCR-ABL kinase domain mutations. In preclinical studies, 40 nM was determined as the concentration of ponatinib sufficient to inhibit viability of cells expressing all tested BCR-ABL mutants by > 50% (including T315I). In a cell-based accelerated mutagenesis assay, no mutation in BCR-ABL was detected that could confer resistance to 40 nM ponatinib.

Ponatinib elicited tumour shrinkage and prolonged survival in mice bearing tumours expressing native or T315I-mutant BCR-ABL.

The dose intensity-safety relationship indicated that there are significant increases in grade 3 or greater adverse events (arterial thrombosis, cardiac failure, hypertension, thrombocytopenia, pancreatitis, neutropenia, rash, ALT increase, AST increase, lipase increase, myelosuppression, arthralgia) over the dose range of 15 to 45 mg once daily.

In the phase 1 study, plasma steady state trough concentrations of ponatinib typically exceeded 21 ng/mL (40 nM) at doses of 30 mg or greater. At daily oral doses of 15 mg or greater, 32 of 34 patients (94%) demonstrated a ≥ 50% reduction of CRKL phosphorylation, a biomarker of BCR-ABL inhibition, in peripheral blood mononuclear cells.

Cardiac Electrophysiology

The effect of ICLUSIG on ECG intervals was assessed in 39 leukemia patients who received 30 mg, 45 mg, or 60 mg ICLUSIG once daily in an open label, uncontrolled trial. Serial ECGs in triplicate were collected at baseline and at 2h, 4h, and 6h post-dosing at steady state (Day 29). The QTcF interval showed a decrease from baseline in all dose cohorts. At the therapeutic dose of 45 mg, the maximal observed mean change in QTcF from baseline was -7.5 ms at 6h.

No large changes in the mean QTc interval (i.e., > 20 ms) from baseline were detected in the study. However, an increase in the mean QTc interval of < 10 ms cannot be excluded because of study design limitations, and due to the absence of a thorough QT study.

Ventricular Performance

The effect of ICLUSIG on LVEF was assessed by echocardiography in 24 patients with advanced or refractory leukemia who received 45 mg ICLUSIG once daily in the phase 1 open-label, uncontrolled trial. The mean change from baseline to minimum post-baseline LVEF was -9.9% (90% CI -13.0, -6.8). Minimum post-baseline ejection was < 50% in 5 (20.8%) of the subjects and < 40% in 2 (8.3%) subjects. The reduction from baseline to minimum post-baseline ejection fraction was ≥ 10% in 10 (41.7%) subjects, including 3 (12.5%) subjects with a reduction from baseline of ≥ 20%.

10.3 Pharmacokinetics

Table 10. Summary of Ponatinib Pharmacokinetic Parameters at Steady State

Dose	C_{max} (ng/mL) [a]	T_{max} (h) [b]	$t_{½}$ (h) [a]	$AUC_{0-\tau}$ (ng.hr/mL) [a]	CL/F (L/h) [c]	V/F (L) [a]
45 mg	73	6	22	1253	34	1101

a: geometric mean; b: median; c: based on a population PK analysis

Absorption:

Peak concentrations of ponatinib are observed approximately 6 hours after oral administration. Within the range of clinically relevant doses evaluated in patients (15 mg to 60 mg), ponatinib exhibited approximately dose-proportional increases in both C_{max} and AUC.

The geometric mean (CV%) C_{max} and $AUC_{(0-\tau)}$ exposures achieved for ponatinib 45 mg daily at steady state were 73 ng/mL (61%) and 1253 ng·hr/mL (58%), respectively. The absolute bioavailability of ponatinib is unknown.

Following either a high-fat or low-fat meal in 22 healthy volunteers, plasma ponatinib exposures (C_{max} and AUC) were not different versus those in fasting conditions. ICLUSIG may be administered with or without food.

Distribution:

In vitro, ponatinib is highly bound (> 99%) to plasma proteins. The blood/plasma partition ratio of ponatinib is 0.96. At daily doses of 45 mg, the geometric mean (CV%) apparent steady state volume of distribution is 1101 L (94%), suggesting that ponatinib is extensively distributed in the extravascular space. *In vitro* studies suggested that ponatinib is either not a substrate or is a weak substrate for both P-gp and BCRP. Ponatinib is not a substrate for the organic anion transporting polypeptides OATP1B1, OATP1B3, or the organic cation transporter OCT-1.

Metabolism:

Ponatinib is metabolized to an inactive carboxylic acid by esterases and/or amidases, and metabolized by CYP3A4 to an N-desmethyl metabolite that is 4 times less active than ponatinib. The carboxylic acid and the N-desmethyl metabolite comprise 58% and 2% of the circulating levels of ponatinib, respectively.

Elimination:

Following multiple 45 mg doses of ICLUSIG in patients, the terminal elimination half-life of ponatinib was 22 hours. With once daily dosing, plasma exposures of ponatinib are increased by approximately 1.5-fold between first dose and steady state conditions. Ponatinib is mainly eliminated via feces. Following a single oral dose of [^{14}C] ponatinib, approximately 87% of the radioactive dose is recovered in the feces and approximately 5% in the urine. Unchanged ponatinib accounted for 24% and < 1% of the administered dose in feces and urine, respectively, with the remainder of the dose comprising metabolites.

Linearity/Non-linearity:

A pharmacokinetic analysis conducted on the plasma concentration-time data from the 81 patients in the phase 1 study (AP24534-07-101) showed the increase in ponatinib concentrations was approximately proportional with increasing dose over the 15 mg to 60 mg dose range.

Special Populations and Conditions

No specific studies have been performed to evaluate the effects of gender, age, race, and body weight on ponatinib pharmacokinetics. In CP-CML patients 65 years of age and over, there was a trend towards reduced efficacy.

- **Hepatic Insufficiency**

A single 30 mg oral dose of ponatinib was administered to subjects with normal liver function (N=8) and to subjects with mild [Child-Pugh A (N=6)], moderate [Child-Pugh B (N=6)], and severe [Child-Pugh C

(N=4)] hepatic impairment. Compared to subjects with normal liver function, there was no trend of increased ponatinib exposure in subjects with hepatic impairment.

There was an increased incidence of adverse reactions in patients with severe hepatic impairment compared to subjects with normal liver function. Caution is recommended when administering ICLUSIG to patients with hepatic impairment. The recommended starting dose is 30 mg once daily in patients with hepatic impairment (Child-Pugh A, B, or C) (see 7.1.7 Hepatic Impairment).

- **Renal Insufficiency**

Renal excretion is not a major route of ponatinib elimination. ICLUSIG has not been studied in patients with severe renal impairment (creatinine clearance <30 mL/min). Caution is recommended when administering ICLUSIG to patients with severe renal impairment or end-stage renal disease (see 7.1.8 Renal Impairment).

Mild to moderate renal impairment (creatinine clearance 30 to 89 mL/min) did not have a clinically meaningful effect on the pharmacokinetics of ponatinib based on a population pharmacokinetic analysis.

- **Pharmacogenomics**

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product (see 7.1.6 Lactose Intolerance and 2 CONTRAINDICATIONS).

11 STORAGE, STABILITY AND DISPOSAL

ICLUSIG tablets should be stored at room temperature (15° to 30°C).

Store in the original package.

ICLUSIG must be kept out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

No special requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

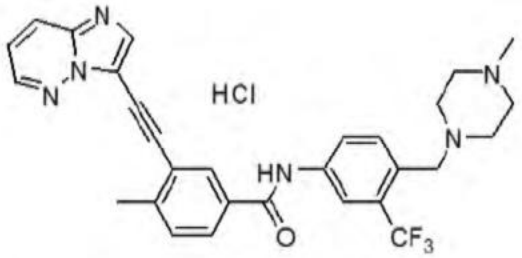
Proper name: ponatinib HCl

Chemical name: 3-(imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}benzamide hydrochloride

Molecular formula and molecular mass: $C_{29}H_{28}ClF_3N_6O$ 569.02 g/mol (salt)

$C_{29}H_{27}F_3N_6O$ 532.56 g/mol (free base)

Structural formula:



Physicochemical properties: Ponatinib HCl is an off-white to yellow powder with pKa of 2.77 and 7.8. The solubility of ponatinib in pH 1.7, 2.7, and 7.5 buffers is 7790 mcg/mL, 3.44 mcg/mL, and 0.16 mcg/mL, respectively, indicating a decrease in solubility with increasing pH.

Pharmaceutical standard: Professed

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)

Table 11. Summary of Patient Demographics for Clinical Trials with ICLUSIG

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age in years (Range)	Sex, n (%) M/F
AP24534-10-201 (PACE)	Multicenter, single-arm, open-label phase 2 study	Starting dose of ponatinib: 45 mg taken orally once daily with possible dose modification including dose reduction to 15 mg or 30 mg once daily	n=449 patients with CML (CP, AP, or BP) or Ph+ ALL, resistant or intolerant to dasatinib or nilotinib, or had T315I mutation	59 (18 - 94) (median)	238 (53%) / 211 (47%)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age in years (Range)	Sex, n (%) M/F
AP24534-14-203 (OPTIC)	Multicenter, randomized, open-label, phase 2 study	Cohort A: 45 mg taken orally once daily	n=94	48.3 (18 – 81)	141 (50%) / 141 (50%)
		Cohort B: 30 mg taken orally once daily	n=94		
		Cohort C: 15 mg taken orally once daily	n=94		
			Total=282 Patients with CP-CML, resistant or who had T315I mutation		

Previously Treated CML or Ph+ ALL (PACE)

The safety and efficacy of ICLUSIG (ponatinib tablets) in adult CML and Ph+ ALL patients who were resistant or intolerant to prior TKI therapy were evaluated in 449 patients in a single-arm, open-label, international, multicenter phase 2 trial (PACE study). All patients were administered a starting dose of 45 mg of ICLUSIG once daily with the possibility of dose modifications, dose reductions, and/or interruptions. Patients were assigned to one of 6 cohorts based on disease phase (CP-CML; AP-CML; or BP-CML/Ph+ ALL), resistance or intolerance (R/I) to dasatinib or nilotinib, or the presence of the T315I mutation. Resistance in CP-CML was defined as failure to achieve either a complete hematologic response (CHR) (by 3 months), a minor cytogenetic response (by 6 months), or a major cytogenetic response (MCyR) (by 12 months) while on dasatinib or nilotinib.

CP-CML patients who experienced a loss of response or development of a kinase domain mutation in the absence of a complete cytogenetic response or progression to AP-CML or BP-CML at any time on dasatinib or nilotinib were also considered resistant. Resistance in AP-CML and BP-CML/Ph+ ALL was defined as failure to achieve either a major hematologic response (MaHR) (AP-CML by 3 months, BP-CML/Ph+ ALL by 1 month), loss of MaHR (at any time), or development of kinase domain mutation in the absence of a MaHR while on dasatinib or nilotinib.

Intolerance was defined as the discontinuation of dasatinib or nilotinib due to toxicities despite optimal management in the absence of a complete cytogenetic response (CCyR) for CP-CML patients or MaHR for AP-CML, BP-CML, or Ph+ ALL patients.

The primary efficacy endpoint in CP-CML was MCyR by 12 months which included CCyR and partial cytogenetic responses (PCyR)[1]. The secondary efficacy endpoints in CP-CML were CHR and major molecular response (MMR). The primary efficacy endpoint in AP-CML and BP-CML/Ph+ ALL was MaHR by 6 months, defined as either a CHR or no evidence of leukemia (NEL). The secondary efficacy endpoints in AP-CML and BP-CML/Ph+ ALL were MCyR and MMR. For all patients, additional secondary

[1] In PACE, a month is defined as 30.43 days for all calculations.

efficacy endpoints included confirmed MCyR, time to response, duration of response, progression-free survival (PFS), and overall survival (OS).

The phase 2 PACE trial enrolled 449 patients, of which 444 were eligible for analysis: 267 CP-CML patients (R/I Cohort: n=203, T315I Cohort: n=64), 83 AP-CML patients (R/I Cohort: n=65, T315I Cohort: n=18), 62 BP-CML (R/I Cohort: n=38, T315I Cohort: n=24), and 32 Ph+ ALL patients (R/I Cohort: n=10, T315I Cohort: n=22). A prior MCyR or better (MCyR, MMR, or complete molecular response [CMR]) to dasatinib or nilotinib was only achieved in 26% patients with CP-CML, and a prior MaHR or better (MaHR, MCyR, MMR, or CMR) was only achieved in 21% and 24% of AP-CML and BP-CML/Ph+ ALL patients, respectively. Baseline demographic characteristics are described in Table 12 below.

Table 12. Demographics and Disease Characteristics for PACE

Patient Characteristics at Entry	Total Safety Population N=449
Age	
Median, years (range)	59 (18 - 94)
Gender, n (%)	
Male	238 (53%)
Race, n (%)	
Asian	59 (13%)
Black/African American	25 (6%)
White	352 (78%)
Other	13 (3%)
ECOG Performance Status, n (%)	
ECOG=0 or 1	414 (92%)
Disease History	
Median time from diagnosis to first dose, years (range)	6.09 (0.33 - 28.47)
Resistant to prior TKI therapy[a], n (%)	374 (88%)
Prior TKI therapy– number of regimens, n (%)	
1	31 (7%)
2	155 (35%)
≥3	263 (59%)
BCR-ABL mutation detected at entry[b], n (%)	
None	198 (44%)
1	192 (43%)
≥2	54 (12%)

[a] Of 427 patients reporting prior tyrosine kinase inhibitor (TKI) therapy with dasatinib or nilotinib.

[b] Of the patients with one or more BCR-ABL kinase domain mutations detected at entry, 37 unique mutations were detected.

Study Results in Previously Treated CML or Ph+ ALL (PACE)

Overall, 56% of patients had one or more BCR-ABL kinase domain mutation at entry, with the most frequent being T315I (29%), F317L (8%), E255K (4%) and E359V (4%). In 67% of CP-CML patients in the R/I cohort, no mutations were detected at study entry. The median duration of follow-up for all patients was 37.3 months (range: 0.07 to 73.1 months); 56.8 months for CP-CML patients, 32.3 months for AP-CML patients, and 6.0 months for patients with BP-CML/Ph+ ALL. The median duration of ICLUSIG treatment was 32.2 months in CP-CML patients, 19.4 months in AP-CML patients, 2.9 months in BP-CML patients, and 2.7 months in Ph+ ALL patients. Efficacy results are summarized in Table 13 and Table 14.

Table 13. Efficacy of ICLUSIG in Resistant or Intolerant CP-CML Patients in PACE (N=449)

	Overall (N=267)[a]	Resistant or Intolerant	
		R/I Cohort (N=203)	T315I Cohort (N=64)
Cytogenetic Response Rate			
Major (MCyR)[b] % n/N 95% CI (%)	55% (148/267) (49 - 62)	51% (103/203) (44 - 58)	70% (45/64) (58 - 81)
Complete (CCyR) % n/N 95% CI (%)	46% (123/267) (40 - 52)	40% (81/203) (33 - 47)	66% (42/64) (53 - 77)
Major Molecular Response (MMR)[c] % n/N 95% CI (%)	40% (108/267) (35 - 47)	35% (71/203) (28 - 42)	58% (37/64) (45 - 70)

MCyR rates are unconfirmed (defined as response not necessarily confirmed at subsequent assessment).

[a] Includes 3 CP-CML patients who were not assigned to a cohort. These patients had a history of T315I that was not confirmed by mutation testing at study entry, and did not have prior therapy with either dasatinib or nilotinib.

[b] Primary endpoint for CP-CML Cohorts was MCyR (unconfirmed) by 12 months, which combines both complete (No detectable Ph+ cells) and partial (1% to 35% Ph+ cells) cytogenetic responses.

[c] Secondary endpoint for CP-CML Cohorts was MMR measured in peripheral blood. Defined as a ≤ 0.1% ratio of BCR-ABL to ABL transcripts on the International Scale (IS) (i.e., ≤ 0.1% BCR-ABL^{IS}; patients must have the b2a2/b3a2 [p210] transcript), in peripheral blood, measured by quantitative reverse transcriptase polymerase chain reaction (qRT PCR).

Ninety-four percent (95% CI: [91% - 97%]) of CP-CML patients achieved a CHR. The estimated median time to CHR was 13 days.

Of the CP-CML patients previously treated with 1, 2, 3 or 4 prior market authorised TKIs, 79% (15/19), 68% (66/97), 44% (63/142), and 58% (7/12) achieved a MCyR while on ICLUSIG, respectively.

Of the CP-CML patients with no mutation detected at entry, 49% (66/136) achieved a MCyR. In CP-CML patients who achieved confirmed MCyR (defined as CCyR [no Ph+ cells] + PCyR [1% to 35% Ph+ cells]),

the median time to MCyR was 2.8 months (range: 1.6 to 11.3 months) and in patients who achieved MMR, the median time to MMR was 5.5 months (range: 1.8 to 55.5 months).

Of the CP-CML patients, 59.6% (159/267), 53.9% (144/267), and 40.4% (108/267) achieved MCyR, CCyR, and MMR, respectively, at any time on study. Most of the CP-CML patients who achieved MMR (40.4%, 108/267) also achieved MR4 (30.3%, 81/267) or MR4.5 (24.0%, 64/267).

The median durations of MCyR and MMR had not yet been reached at data cutoff. Of the CP-CML patients who achieved MCyR and MMR, 82.4% (95% CI: [74.1% – 88.2%]) and 61.0% (95% CI: [50.6% – 69.8%]), respectively, were estimated to maintain their response after 5 years.

With a median follow-up of 56.8 months, 3.4% (9/267) of CP-CML patients experienced transformation of their disease to AP-CML or BP-CML.

Based on Kaplan-Meier estimates, CP-CML patients who achieved certain MCyR or MMR response within the first year of treatment had statistically significantly improved PFS and OS compared to those patients who did not meet the treatment milestones.

Table 14. Efficacy of ICLUSIG in Resistant or Intolerant AP-CML, BP-CML or Ph+ ALL Patients in PACE

	AP-CML		BP-CML		Ph+ ALL	
	R/I Cohort (N=65)	T315I Cohort (N=18[a])	R/I Cohort (N=38)	T315I Cohort (N=24)	R/I Cohort (N=10)	T315I Cohort (N=22)
Hematologic Response Rate						
Major (MaHR)[b]						
%	57%	56%	32%	29%	50%	36%
n/N	(37/65)	(10/18)	(12/38)	(7/24)	(5/10)	(8/22)
95% CI (%)	(44 – 69)	(31 – 79)	(18 – 49)	(13 – 51)	(19 – 81)	(17 – 59)
Complete (CHR)[c]						
%	49%	56%	24%	17%	40%	32%
n/N	(32/65)	(10/18)	(9/38)	(4/24)	(4/10)	(7/22)
95% CI (%)	(37 - 62)	(31 – 79)	(11 – 40)	(5 – 37)	(12 – 74)	(14 – 55)
Major Cytogenetic Response (MCyR)[d]						
%	34%	56%	18%	29%	60%	41%
n/N	(22/65)	(10/18)	(7/38)	(7/24)	(6/10)	(9/22)
95% CI (%)	(23 – 47)	(31 – 79)	(8 – 34)	(13 – 51)	(26 – 88)	(21 – 64)

[a] Includes 2 AP-CML patients who were not assigned to a cohort. These patients had a history of T315I that was not confirmed by mutation testing at study entry, and did not have prior therapy with either dasatinib or nilotinib.

[b] Primary endpoint for AP-CML and BP-CML/Ph+ ALL cohorts was MaHR by 6 months, which combines complete hematologic responses and no evidence of leukemia.

[c] CHR (confirmed): WBC ≤ institutional ULN, ANC ≥1000/mm^3, platelets ≥100,000/mm^3, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils <5% in peripheral blood, no extramedullary involvement (including no hepatomegaly or splenomegaly).

[d] MCyR combines both complete (no detectable Ph+ cells) and partial (1% to 35% Ph+ cells) cytogenetic responses.

The median time to MaHR in patients with AP-CML, BP-CML, and Ph+ ALL among responders was 0.7 months (range: 0.4 to 5.8 months), 1.0 month (range: 0.4 to 3.7 months), and 0.7 months (range: 0.4 to 5.5 months), respectively.

The median duration of MaHR for patients with AP-CML, BP-CML and Ph+ ALL was estimated as 12.9 months (range: 1.2 to 68.4 months), 6.0 months (range: 1.8 to 59.6 months), and 3.2 months (range: 1.8 to 12.8 months), respectively. In the patients with AP-CML, the probability of remaining in MaHR was estimated to be 51% (95% CI: [36% - 65%]) and 29% (95% CI: [17% - 43%]) at 12 months and 24 months, respectively. In the patients with BP-CML/Ph+ ALL, the probability of remaining in MaHR was estimated to be 28% (95% CI: [14% - 44%]) and 16% (95% CI: [6% - 30%]) at 12 months and 24 months, respectively.

Previously Treated CP-CML (OPTIC)

The safety and efficacy of ICLUSIG was evaluated in a randomized, open-label, phase 2 dose-optimization trial in adult CP-CML patients whose disease was considered to be resistant to at least 2 prior TKIs or who had the T315I mutation (OPTIC study). Resistance in CP-CML while on a prior TKI was defined as failure to achieve either a CHR (by 3 months), a minor cytogenetic response (by 6 months), a MCyR (by 12 months), or development of a new BCR-ABL1 kinase domain mutation or new clonal evolution. Patients were required to have >1% BCR-ABL1^{IS} (by real-time polymerase chain reaction) at trial entry. Patients received 1 of 3 starting dosages once daily: 45 mg, 30 mg, or 15 mg. Patients who received a starting dose of 45 mg or 30 mg had a dose reduction to 15 mg once daily upon achieving ≤1% BCR-ABL1^{IS}.

The primary efficacy endpoint was a molecular response based on the achievement of ≤1% BCR-ABL1^{IS} at 12 months (defined as a ≤1% ratio of BCR-ABL to ABL transcripts on the International Scale (IS))[2]. All patients reached the 12-month time point (primary endpoint) by the data cutoff.

The secondary efficacy endpoints included CCyR at 12 months, MMR at 12 and 24 months, CHR at 3 months, time to response, duration of response, maintenance of response, PFS and OS. Additional assessment included the rates of molecular response at each patient visit at 3-month intervals for 36 months based on the achievement of ≤1% BCR-ABL1^{IS}.

Baseline demographic characteristics are described in Table 15 for patients who received a starting dose of 45 mg.

[2] In OPTIC, a month is defined as 28 days (cycle of treatment for ICLUSIG) for all calculations.

Table 15. Demographic and Disease Characteristics for OPTIC (45 mg Cohort)

Patient Disease Characteristics at Entry	ICLUSIG 45 mg → 15 mg (N=94)
Age	
Median years (range)	46 (19 to 81)
Sex, n (%)	
Male	50 (53%)
Race, n (%)	
White	73 (78%)
Asian	16 (17%)
Other/Unknown	4 (4%)
Black or African American	1 (1%)
ECOG Performance Status, n (%)	
ECOG 0 or 1	93 (99%)
Disease History	
Median time from diagnosis to first dose, years (range)	5.5 (1 to 21)
Resistant to Prior Kinase Inhibitor, n (%)	92 (98%)
Presence of one or more BCR-ABL kinase domain mutations, n (%)	41 (44%)
Number of Prior Kinase Inhibitors, n (%)	
1	1 (1%)
2	43 (46%)
≥3	50 (53%)
T315I mutation at baseline	25 (27%)
Comorbidities	
Hypertension	29 (31%)
Diabetes	5 (5%)
Hypercholesterolemia	3 (3%)
History of ischemic heart disease	3 (3%)

Study Results in Previously Treated CP-CML (OPTIC)

The median duration of follow-up for the 45 mg cohort (N=94) was 31.1 months (95% CI: 24.1, 36.0). A total of 282 patients received ICLUSIG: 94 received a starting dose of 45 mg, 94 received a starting dose of 30 mg, and 94 received a starting dose of 15 mg.

Efficacy results are summarized in Table 16. The primary endpoint was met in patients who received a starting dose of 45 mg. Overall, 44% of patients had one or more BCR-ABL kinase domain mutations at study entry with the most frequent being T315I (27%). The subgroup analysis based on baseline T315I mutation status showed similar ≤1% BCR-ABL1^{IS} rates at 12 months in patients with and without T3151. No mutations were detected at study entry for 54% of the patients who received the starting dose of 45 mg.

Table 16. Efficacy Results in Patients with CP-CML who Received ICLUSIG at Starting Dose of 45 mg in OPTIC

	ICLUSIG 45 mg → 15 mg (N=93)[a]
Molecular Response at 12 months[b]	
Overall ≤1% BCR-ABL1^{IS} Rate % (n/N) (98.3% CI)[c]	 44% (41/93) (32%, 57%)
Patients with T315I mutation % (n/N) (95% CI)	 44% (11/25) (24%, 65%)
Patients without T315I mutation % (n/N) (95% CI)	 44% (29/66)[d] (32%, 57%)
Cytogenetic Response by 12 months	
Major (MCyR)[e] % (n/N) (95% CI)	 48% (44/91)[f] (38%, 59%)
Patients with T315I mutation % (n/N) (95% CI)	 52% (13/25) (31%, 72%)
Patients without T315I mutation % (n/N) (95% CI)	 46% (30/65)[g] (34%, 59%)

[a] ITT population (N=93) defined as patients who had b2a2/b3a2 BCR ABL1 transcripts.

[b] Primary endpoint was ≤1% BCR-ABL1^{IS} rate at 12 months. Defined as a ≤1% ratio of BCR ABL to ABL transcripts on the International Scale (IS) (i.e., ≤1% BCR-ABL^{IS}; patients must have the b2a2/b3a2 (p210) transcript), in peripheral blood measured by quantitative reverse transcriptase polymerase chain reaction (qRT PCR).

[c] 98.3% CI is calculated using the binomial exact (Clopper-Pearson) method.

[d] Of the 93 patients, two patients did not have a baseline mutation assessment and were excluded from the response by mutation analysis.

[e] Secondary endpoint was MCyR by 12 months which combines both complete (no detectable Ph+ cells) and partial (1% to 35% Ph+ cells in at least 20 metaphases) cytogenetic responses.

[f] Analysis is based on ITT cytogenetic population (N=91) defined as patients who had a cytogenetic assessment at baseline with at least 20 metaphases examined. One patient who had a complete cytogenetic response at baseline was excluded from the analysis.

[g] Of the 91 patients, one patient did not have a baseline mutation assessment and was excluded from the response by mutation analysis.

At 12 months, 34% (31/91) and 17% (16/93) of CP-CML patients who received a starting dose of 45 mg achieved CCyR, and MMR, respectively. At 24 months, 24% (18/75) of patients achieved MMR. The median duration of MMR had not yet been reached. Eighty-seven percent (95% CI: [79% - 93%]) patients achieved or maintained a CHR at 3 months.

A response of ≤1% BCR-ABL1^{IS} was achieved as early as 2.9 months. In CP-CML patients who received a starting dose of 45 mg, the median time to response was 6 (95% CI: 3.1, 6.0) months. The median duration of ICLUSIG treatment in patients who received a starting dose of 45 mg was 21 months. Of the

45 patients who had a dose reduction after achieving ≤1% BCR-ABL1^{IS}, 28 patients (62%) maintained their response at the reduced dose for at least 90 days. Of the 28 patients, 18 patients (64%) maintained the response for at least one year. Median duration of response (MR2) was not reached at data cutoff.

Long-term outcomes (PFS and OS) were favourable. Based on Kaplan-Meier estimates, the PFS rates were 92% at 12 months and 80% at 24 months. The OS rates were 98% at 12 months and 92% at 24 months.

The rates of efficacy response ≤1% BCR-ABL1^{IS} analysed by patient visits at pre-specified timepoints were 22% (3 months), 41% (6 months), 47% (9 months), 52% (12 months), 56% (18 months), 56% (24 months), 56% (30 months) and 56% (36 months).

The molecular response rates (measured by achievement of ≤1% BCR-ABL1^{IS}) at 12 months was lower among patients who had received treatment with ≤2 prior TKIs compared with patients who had received ≥3 prior TKIs (40% vs 48%, respectively).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Single-dose Toxicity

In mice, single doses of 50 and 150 mg/kg ponatinib were asymptomatic. At 450 mg/kg, rough hair coats, reversible decreased body weight gain, and decreased food consumption were observed. The no-observed-adverse-effect level (NOAEL) for ponatinib was 150 mg/kg when administered as a single oral dose to mice.

Rats administered single oral doses of 10 mg/kg ponatinib were asymptomatic, except for thinning fur in one animal/sex. Transient decreases in reticulocytes, albumin and A:G ratio were noted. At doses of 30 and 100 mg/kg, histopathologic examination revealed that moribundity and mortality in many of these animals appeared to be associated with ponatinib-mediated immunosuppression (due to lymphoid depletion). Bacterial sepsis was a sequela to the immunosuppression, and there were numerous systemic tissue alterations that were deemed secondary to sepsis/hypoperfusion/shock. In addition, single-cell necrosis involving the exocrine pancreas and intestinal crypt epithelial cells was observed at 100 mg/kg. Clinical signs were also observed in the 30 and 100 mg/kg dose groups. The NOAEL for ponatinib was 10 mg/kg when administered as a single oral dose to rats.

Ponatinib doses of 5, 15, and 45 mg/kg administered to cynomolgus monkeys were well tolerated; the only noteworthy clinical observations were dry flaky skin and mild to moderate skin erythema at 15 and 45 mg/kg. Reversible, slight body weight loss and reduced food consumption were observed at the 15 and 45 mg/kg doses during the first week post-dose. There were no ponatinib-related changes in hematology, clinical chemistry, coagulation, or urinalysis parameters. Systolic heart murmurs were noted in individual animals treated with 5 and 45 mg/kg. Heart murmurs were also noted in some animals near the end of a 28-day repeat dose toxicity study on ponatinib in cynomolgus monkeys that were shown to be reversible. In both studies, no macroscopic or microscopic correlates were noted.

Repeat-dose Toxicity

Pivotal repeat-dose toxicity studies were conducted in rats and cynomolgus monkeys. In the 28-day study in rats, animals were administered doses of 0, 1.5, 3 and 6 mg/kg ponatinib and in the 6-month study in rats, doses of 0, 0.25, 0.75, and 2 mg/kg were administered. In the 28-day rat study, there were transient increases in mean ALT and AST, however, there were microscopic correlates. Dry flaky skin was observed in rats after repeated dosing.

In monkeys, ponatinib doses were 0, 1, 2.5, and 5 mg/kg in the 28-day study, and 0, 0.25, 0.75, and 2 mg/kg in the 6-month study. The pancreas was identified as a target organ of toxicity in the 28-day toxicity study in monkeys. Skin changes in the form of crusts, hyperkeratosis, or erythema were observed in toxicity studies in cynomolgus monkeys. Heart murmurs were observed in individual animals in the repeat-dose 28-day toxicity study. In the 6-month study, there were reversible increases in ALT/AST levels in individual animals without microscopic correlates.

In addition, the adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use are described below. Depletion of lymphoid organs was observed in repeat-dose toxicity studies in rats and cynomolgus monkeys. The effects were shown to be reversible or partially reversible after withdrawal of the treatment. Ponatinib-related bone changes were observed in repeat-dose toxicity studies in rats and characterized by reversible hyperplasia of the epiphyseal cartilage after 28 days of administration, and a non-reversible reduction in physeal chondrocytes after 6 months of administration.

In rats, inflammatory changes accompanied by increases in neutrophils, monocytes, eosinophils, and fibrinogen levels were found in the preputial and clitoral glands following chronic dosing. Thyroid gland follicular atrophy mostly accompanied by a reduction in T3 levels and a tendency toward increased TSH and T4 levels were observed in the 4-week repeat-dose toxicity study in cynomolgus monkeys and reversible reductions in T3 levels with no microscopic correlates in rats.

Ponatinib at doses of 3, 10, and 30 mg/kg produced increases in urine output and electrolyte excretions and caused a decrease in gastric emptying in safety pharmacology studies in rats.

Carcinogenicity:

In a two-year carcinogenicity study, male rats were orally administered ponatinib at 0.05, 0.1 and 0.2 mg/kg/day and females were orally administered 0.2, 0.4, and 0.8 mg/kg/day. A statistically significant increased incidence of squamous cell carcinoma of the clitoral gland was observed at 0.8 mg/kg/day, which resulted in plasma exposure levels generally lower or equivalent to human exposure at a dose range of 15 to 45 mg daily. At doses of 0.4 and 0.8 mg/kg/day, there was increased incidence of sex cord stromal hyperplasia and of mixed sex cord stromal benign tumours in the ovaries. The clinical relevance of these findings is not known.

Genotoxicity:

Ponatinib was not mutagenic in a bacterial mutagenesis (Ames) assay, was not clastogenic in a chromosome aberration assay in human lymphocytes, nor was it clastogenic in an *in vivo* mouse micronucleus assay at oral doses up to 2000 mg/kg.

Reproductive and Developmental Toxicology:

Ponatinib may impair fertility in female patients. In a rat fertility study with 0.25, 0.75, and 1.50 mg/kg/day ponatinib, there was no effect observed on male fertility parameters, but female fertility parameters were reduced. There was increased pre- and post-implantation embryo-fetal lethality observed in the 1.50 mg/kg/day female group. The NOAEL for paternal toxicity was

0.25 mg/kg/day based on reduced body weight and reduced body weight gain at ≥0.75 mg/kg/day. The NOAEL for reproductive performance and fertility was 1.50 mg/kg/day in males and 0.75 mg/kg/day in females.

Ponatinib was administered orally to pregnant female rats at doses of 0.3, 1, and 3 mg/kg/day from Gestation Day 7 through 17. Embryo-fetal toxicity in the form of post-implantation loss, reduced fetal body weight, and multiple soft tissue and skeletal alterations were observed at maternal toxic dosages. Multiple fetal soft tissue and skeletal alterations were also observed at maternal nontoxic dosages. The maternal NOAEL was considered to be 1 mg/kg/day and the developmental NOAEL was considered to be 0.3 mg/kg/day.

In juvenile rats, daily oral administration of 3 mg/kg/day ponatinib to juvenile rats beginning on Day 15 postpartum resulted in mortality related to inflammatory effects within 6 to 7 days of treatment initiation. Lower doses (0.75 and 1.5 mg/kg/day) caused adverse reductions in body weight gain, but no adverse effects on juvenile rat developmental parameters (vaginal opening, preputial separation or bone measurements).

Ponatinib-related microscopic findings in the ovaries (increased follicular atresia), uterus (endometrial atrophy), and testes (minimal germ cell degeneration) in cynomolgus monkeys treated with 5 mg/kg ponatinib were noted in the 28-day repeat-dose toxicity study at exposures approximately 3.3 times the AUC in patients receiving the recommended dose of 45 mg/day.

Other Toxicity Studies

In a phototoxicity study in rats, diffuse corneal edema with neutrophilic cell infiltration, and hyperplastic changes in the lenticular epithelium suggestive of a mild phototoxic reaction were observed in animals treated with 5 and 10 mg/kg ponatinib.

Ponatinib inhibited aggregation of human platelets in vitro only at a test concentration 100 times higher than the estimated plasma C_{max} in human patients at the recommended therapeutic dose. No inhibition of platelet aggregation was detected at concentrations 10 times higher than the therapeutic C_{max}.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrICLUSIG®

Ponatinib Tablets

Read this carefully before you start taking **ICLUSIG** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ICLUSIG**.

Serious Warnings and Precautions

ICLUSIG can only be prescribed by a doctor:

- who is certified by the **ICLUSIG Controlled Distribution Program**
- who diagnoses and treats leukemia
- who has anti-cancer drug experience

Serious side effects with ICLUSIG include the following:

- Arterial occlusive events. These happen when arteries are narrowed or blocked. These may lead to serious side effects, sometimes leading to amputation or death.
- Blood clots in the veins (deep vein thrombosis) especially in the legs which may travel through blood vessels to the lungs (pulmonary embolism). These may lead to death.
- Heart problems that may lead to death.
- Bleeding that may lead to death.
- Liver problems that may lead to death.
- Myelosuppression, which is a decreased production of blood cells.
- Pancreatitis, which is inflammation of your pancreas.

What is ICLUSIG used for?

ICLUSIG is used to treat adults with chronic myeloid leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). These patients will have leukemia that no longer benefits from treatment with other medicines.

This medicine is available through the **ICLUSIG Controlled Distribution Program.** More details on the ICLUSIG Controlled Distribution Program are located at the end of this Patient Medication Information.

How does ICLUSIG work?

ICLUSIG belongs to a group of medicines called tyrosine kinase inhibitors. In patients with CML and Ph+ ALL, the body produces abnormal white blood cells. ICLUSIG blocks a signal and stops the production of these abnormal white blood cells.

What are the ingredients in ICLUSIG?

Medicinal ingredients: Ponatinib

Non-medicinal ingredients: Colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sodium starch glycolate, talc, titanium dioxide

ICLUSIG comes in the following dosage forms:

Tablets; 15 mg and 45 mg ponatinib (as ponatinib hydrochloride)

Do not use ICLUSIG if:

- you are allergic to ponatinib or to any other ingredient in this medicine or part of the container
- your doctor thinks you are at risk of heart problems
- you have high blood pressure that is not controlled by medication
- you are dehydrated or have severe vomiting, diarrhea, or sweating. This is more important if you have high uric acid in your blood.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ICLUSIG. Talk about any health conditions or problems you may have, including if you:

- have a liver or pancreas disorder, diabetes, or reduced kidney function
- have a history of alcohol abuse
- had a heart attack or stroke before, or surgery to restore blood supply after a blockage
- had a recent surgery or plan to have a medical procedure
- have a history of bleeding issues
- have a history of blood clots in your blood vessels or heart problems, including heart failure, angina or irregular heartbeats
- have high blood pressure
- have a history of high cholesterol or fats in your blood (called hypertriglyceridemia)
- have a history of narrowing of the blood vessels to one or both kidneys
- are intolerant to milk sugar, or have one of the following rare hereditary diseases:
  - Galactose intolerance
  - Lapp lactase deficiency
  - Glucose-galactose malabsorption

  This is because lactose is a non-medicinal ingredient in ICLUSIG.
- have ever had or might now have a hepatitis B virus infection (a viral infection of the liver). This is because during treatment with ICLUSIG, hepatitis B virus may become active again, which can be fatal in some cases. Your doctor will check for signs of this infection before and during treatment with ICLUSIG.
- are over 65 years of age, as you may be more likely to have side effects.

Other warnings you should know about:

- **Eye problems** can occur while you are taking ICLUSIG. Tell your doctor without delay if you experience any blurred vision, dry eye, eye pain, or any other eye problem during treatment. You may need tests performed by an eye specialist (ophthalmologist).

Driving and using machines

Before doing tasks that require special attention, wait until you know how you respond to ICLUSIG. Blurred vision, visual disturbance, dizziness, mental status changes, and confusion can occur.

Pregnancy and Breast-Feeding:

Female patients:

- If you are pregnant, planning to get pregnant, or think you are pregnant, there are specific risks you should discuss with your healthcare professional.
- Avoid getting pregnant while you are taking ICLUSIG. It may harm your unborn baby.

- Use effective birth control during your treatment with ICLUSIG. It is not known if ICLUSIG affects how birth control pills work. They may not work as well to prevent pregnancy when taken at the same time as ICLUSIG. Use a different or additional method of birth control during your treatment with ICLUSIG.
- It is not known if ICLUSIG passes into breast milk. Stop breast-feeding during your treatment.

Male patients:

- You should not father a child during your treatment with ICLUSIG.
- Use effective birth control during your treatment.

Fertility (ability to have a child) for women: ICLUSIG may make it harder to get pregnant. This has not been tested in humans.

Tests and check-ups: Before you start ICLUSIG, your healthcare professional will do blood tests and other assessments to check your eyes, heart and blood pressure. They will also test you for hepatitis B virus. If you test positive for hepatitis B virus, you may need to see a liver specialist before you start ICLUSIG.

During your treatment, you will have blood tests. These will be done every 2 weeks for the first few months of treatment or as directed by your doctor. Thereafter, the blood tests will be done about once per month or as directed by your doctor. These tests will tell your healthcare professional how your treatment is affecting your blood, liver and pancreas. Your healthcare professional will also monitor your blood pressure and check you for signs of swelling, blood clots and heart or eye problems.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ICLUSIG:

- medicines to treat fungal, viral (including HIV infection) or bacterial infections such as ketoconazole, itraconazole, voriconazole, posaconazole, nelfinavir, ritonavir, clarithromycin
- an herbal product used to treat depression called St. John's Wort
- a medicine to treat epilepsy, euphoric/depressive stages and certain pain conditions called carbamazepine
- medicines to treat seizures such as phenobarbital, phenytoin
- medicines to treat tuberculosis or certain other infections such as rifabutin, rifampicin
- a medicine to treat heart weakness called digoxin
- a medicine to prevent blood clots called dabigatran
- a medicine to treat gout called colchicine
- medicines to lower high cholesterol levels such as pravastatin, rosuvastatin
- a medicine to treat severe joint inflammation (rheumatoid arthritis), cancer and the skin disease psoriasis called methotrexate
- a medicine to treat severe bowel and rheumatic joint inflammation called sulfasalazine

Avoid eating or drinking any products or juices that contain grapefruit, star fruit, pomegranate, Seville oranges or other similar fruit. They may interact with ICLUSIG.

How to take ICLUSIG:

Take ICLUSIG:

- exactly as your healthcare professional has told you. Ask your doctor, nurse or pharmacist if you are not sure.
- once per day, with or without food.
- Swallow tablet(s) whole, with a glass of water.
- Do NOT crush or dissolve tablet(s).

This is a long-term treatment. Take ICLUSIG daily for as long as it is prescribed. Do not change your dose, unless your healthcare professional tells you to do so.

Usual starting dose: 45 mg once a day. Your starting dose might be lower if you have liver problems.

To make this dose, you may take either one 45 mg tablet or three 15 mg tablets.

Your doctor may reduce your dose or tell you to stop taking this medicine if you experience certain side effects. Your doctor may also adjust your dose based on your response to treatment. Other possible doses are:

30 mg a day: to make this dose, take two 15 mg tablets

15 mg a day: to make this dose, take one 15 mg tablet

Overdose:

If you think you, or a person you are caring for, have taken too much ICLUSIG, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Do not take two doses at the same time or take an extra dose to make up for a forgotten dose. Take your next dose at your usual time.

What are possible side effects from using ICLUSIG?

These are not all the possible side effects you may have when taking ICLUSIG. If you experience any side effects not listed here, tell your healthcare professional.

- headache, dizziness or spinning feeling, ringing in the ears, state of confusion
- inflammation of hair follicles, hair loss
- skin that is red, abnormally darkened, dry, itchy, blistered, peeling, scaly, rash
- fatigue, sleeplessness, lack of energy, weakness, general feeling of being unwell, either emotionally or physically, or a combination of the two (malaise)
- vomiting, diarrhea, abdominal distension, discomfort, indigestion, decreased appetite, weight loss, dehydration, unpleasant taste, dry mouth, inflammation in the mouth, stomach acid reflux, nausea, constipation
- cough, upper airway infection, difficulty producing voice sounds, breathing difficulties, chills, flu-like illness, fever
- dry or inflamed eyes
- hot flush, flushing, night sweats, increased sweating
- pain in bones, arms or legs, back, chest, neck, skeletal system, pain in joint, muscles

- pain in one or both legs when walking or exercising. This pain disappears after some rest.
- muscle spasms
- fluid retention in arms and/or legs
- inability to develop and maintain an erection

ICLUSIG can cause abnormal blood and urine test results. Your doctor will decide when to perform blood and urine tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Abdominal pain		√	
Thrombocytopenia (decreased number of blood cells called platelets): bleeding or easy bruising		√	
Anemia (decreased number of red blood cells): tiredness and lack of energy, shortness of breath, noticeable heartbeats, a pale complexion		√	
Neutropenia (low white blood cell count): fever, often with signs of infection		√	
Hypertension (increase or worsening of existing blood pressure): headache, dizziness, chest pain, or shortness of breath		√	
Hemorrhage (unusual bleeding or bruising of the skin): unusual nose bleed, eye bleeding, coughing or vomiting blood, unusual vaginal bleeding, pink or brown-coloured urine, red or black stools, drowsiness, confusion, headache, change in speech		√	
COMMON			
Heart failure/Left ventricular dysfunction (heart does not pump blood as well as it should): swelling in ankles and legs, shortness of breath, cough, fluid retention, fatigue, lack of appetite, nausea		√	
Pericardial effusion (abnormal accumulation of fluid around the heart): difficult or painful breathing, chest pain, cough, dizziness, rapid heart rate		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Heart weakness, heart attack: pain or discomfort in chest, arms, back, neck, jaw or stomach, shortness of breath		√	
Pulmonary hypertension (high blood pressure that affects the blood vessels in the lungs and the right side of your heart): shortness of breath, fatigue, cough, chest pain, fainting and swelling of ankles and feet		√	
Coronary artery disease (narrowing of the heart blood vessels): uncomfortable pressure, fullness, squeezing or pain in your chest (angina)		√	
Pleural effusion (fluid in the chest): chest pain, cough, fever, hiccups, rapid breathing, shortness of breath		√	
Pancreatitis (inflammation of the pancreas): severe stomach and back pain, nausea and vomiting		√	
Arterial occlusive events (condition where arteries are narrowed or blocked): blood circulation problems, blood clot, chest pain, shortness of breath, weakness on one side of the body, speech problems, leg pain or swelling, pain, cold or numbness in the affected limb, limb may be pale or bluish, may result in amputations or need for surgery to restore blood supply by way of a blood vessel graft		√	
Pneumonia (lung infection): fever, cough, shortness of breath, chills, chest pain, fatigue		√	
Sepsis / septic shock (infection in blood): fever, rapid heart rate and breathing		√	
Arrhythmia (abnormal heart beat): rapid, irregular or slow		√	
Deep vein thrombosis (blood clot in a deep vein): swelling or pain in leg, ankle or foot, warmth or changes in skin color, such as turning pale, red or blue over affected area		√	
Pulmonary embolism (blood clot in a lung artery): chest pain, shortness of breath, cough, rapid breathing		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Stroke (bleeding in the brain due to a burst blood vessel, or a blockage in blood vessels supplying blood to the brain): trouble with speaking and understanding, weakness or numbness of face, arm or leg, trouble with seeing in one or both eyes, dizziness, severe headache, trouble with walking and loss of balance		√	
Neuropathy (damage to nerves): increased or reduced sense of touch, prickling, tingling, itching, numbness and pain in the hands and feet, muscle weakness, difficulty walking, convulsions		√	
UNCOMMON			
Tumour lysis syndrome (the sudden, rapid death of cancer cells due to the treatment): nausea, shortness of breath, abnormal heartbeat, lack of urination, cloudy urine, muscle spasms or twitching, muscle weakness, joint pain, tiredness		√	
Eye disorder: blocked eye veins, dry eye, eye pain, blurred vision, visual disturbance, blindness, or cataract		√	
Stomach bleeding: blood in stool, vomiting blood, dark or tarry stool		√	
Liver damage: yellow skin and whites of eyes, nausea, tiredness, loss of appetite, fever, skin rash, joint pain and inflammation, pain in the upper right abdomen, pale stools and dark or tea-coloured urine		√	
Renal artery stenosis (narrowing of blood vessels supplying blood to the kidneys): high blood pressure, swelling		√	
Acute kidney injury (kidneys stop working): decreased urine, swelling of legs, ankles and/or eyes		√	
RARE			
Artery dissection (tearing in an artery): sudden severe pain in the back, chest or abdomen		√	
Artery aneurysm (a bulge in the wall of any artery including in the chest, arms, legs, heart, and brain):		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Symptoms will differ by the site. There can be cough, coughing up blood. Strong pain high in your neck or in your back when you didn't hurt yourself. Problems swallowing. Hoarse voice. Unusual pulsing in your chest or abdomen.			
Gastrointestinal perforation or fistula (a hole in the wall of the gastrointestinal tract and/or leaking of stomach contents): severe abdominal pain, tenderness, diarrhea, nausea or vomiting, heartburn, bleeding		√	
Poor wound healing		√	
UNKNOWN FREQUENCY			
Hepatitis B Virus Reactivation (a previous viral infection of the liver becomes active again): yellow skin and whites of eyes, nausea, tiredness, loss of appetite, fever, skin rash, joint pain and inflammation, pain in the upper right abdomen, pale stools and dark-coloured urine		√	
Posterior Reversible Encephalopathy Syndrome, PRES – also known as Reversible Posterior Leukoencephalopathy Syndrome, RPLS (a rare neurological disorder): headaches, seizures, confusion, changes in vision or problems thinking		√	
Erythema multiforme (an allergic skin reaction): raised red or purple skin patches, possibly with blister or crust in the center. Possibly swollen lips. Mild itching or burning.		√	
Stevens Johnson syndrome (severe skin reaction): rash, red skin, red or purple skin patches possibly with blister or crust in the center, pus-filled rash, peeling skin, blisters on the lips, eyes, skin or in the mouth, itching, burning, flu-like feeling, fever.		√	
Squamous cell carcinoma (a form of cancer): red bump on the skin, red or scaly patch of skin, a sore that doesn't heal, wart-like sores		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Panniculitis (inflammation of fatty tissue under the skin): painful red lumps, skin pain, skin reddening		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store ICLUSIG at room temperature between 15° to 30°C in the original container.

Keep this medicine out of the reach and sight of children.

Do not use this medicine after the expiry date which is stated on the bottle label after EXP. The expiry date refers to the last day of that month.

If you want more information about ICLUSIG:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website: www.iclusigcdp.ca, or by calling 1-888-867-7426 (English and French).

What does ICLUSIG Controlled Distribution Program mean?

This medicine is available through the ICLUSIG Controlled Distribution Program. Only doctors who have been certified can write a prescription for ICLUSIG.

Pharmacists must be trained and must confirm that your doctor has been certified. The pharmacist cannot fill a prescription for ICLUSIG unless your doctor has been certified.

For information about the ICLUSIG Controlled Distribution Program, please call 1-888-867-7426 (English and French), or visit www.iclusigcdp.ca.

Where can I get my prescription filled?

Only pharmacies that have been trained on ICLUSIG and agree to the ICLUSIG Controlled Distribution Program requirements can fill your prescription. If you need help locating a trained pharmacy please call 1-888-867-7426.

How will my prescription be delivered?

Your prescription will be filled and shipped directly to you by a pharmacist trained in the ICLUSIG Controlled Distribution Program.

What will I receive with each shipment of ICLUSIG?

The pharmacy will mail your prescription of ICLUSIG directly to you along with other important materials, including a

- Patient Medication Guide
- Patient Wallet/Alert Card
- Contact information for the pharmacist

You will receive all of these materials with your first prescription and with each refill.

What is the Patient Alert/Wallet Card and what am I supposed to do with it?

The Patient Alert/Wallet Card contains important information about the serious side effects of ICLUSIG. The Patient Alert/Wallet Card contains information for you, your doctor, or any other healthcare professional involved in your care. You should carry this card with you at all times. Show it to any doctor you consult for any reason.

What if I need more ICLUSIG than what my doctor usually prescribes, such as for travel?

If you need more ICLUSIG, contact your doctor.

What if I lost my medication or my medication was destroyed?

If you need more ICLUSIG, contact your doctor.

How do I contact my trained pharmacist if I have questions?

You may contact your pharmacist by using the contact information that was provided in your ICLUSIG shipment. If you have questions about ICLUSIG, you should also contact your doctor.

This leaflet was prepared by Takeda Pharmaceuticals U.S.A., Inc.

ICLUSIG® is a registered trademark of ARIAD Pharmaceuticals, Inc.

Imported and distributed by: Paladin Labs Inc., Saint-Laurent, QC H4M 2P2

Last Revised OCT 03, 2022

This is **Exhibit "8"** referred to in the Affidavit sworn remotely by Nick Boorman, stated as being at the City of Toronto, in the Province of Ontario, before me at the City of Toronto, in the Province of Ontario, on September 29, 2023, in accordance with O. Reg. 431/20, *Administering Oath or Declaration Remotely*

A Commissioner, etc.

Exhibit “9”

Search results summary

From Health Canada

New search

Search criteria

- Status: Select all
- Product name: iclusig
- Class(es): Select all
- Route(s) of administration: Select all
- Dosage form(s): Select all
- Schedule(s): Select all
- Species: Select all

Search results

Filter items Showing 1 to 2 of 2 entries **Show** 10 **entries**

List of returned drug products

Status	DIN	Company	Product	Class	PM [1]	Schedule	# [2]	A.I. name [3]	Strength
Marketed	02437333	TAKEDA PHARMACEUTICALS U.S.A., INC.	ICLUSIG	Human	Yes	Prescription	1	PONATINIB (PONATINIB HYDROCHLORIDE)	15 MG
Dormant	02437341	TAKEDA PHARMACEUTICALS U.S.A., INC.	ICLUSIG	Human	Yes	Prescription	1	PONATINIB (PONATINIB HYDROCHLORIDE)	45 MG

Table footnotes

1 Product monograph/Veterinary Labelling availability

2 Number of active ingredients

3 Please note that only one active ingredient is displayed per DIN. To see them all, please click on the DIN.

Application information

Search tips
Drug product database terminology
Drug product database data extracts

Related information

MedEffect Canada
Adverse drug reaction - veterinary drugs
Notice of compliance database
Licensed natural health products database

Contact us

Content support
Technical support

Version 4.0.1

Date modified: 2023-05-25

This is **Exhibit "9"** referred to in the Affidavit sworn remotely by Nick Boorman, stated as being at the City of Toronto, in the Province of Ontario, before me at the City of Toronto, in the Province of Ontario, on September 29, 2023, in accordance with O. Reg. 431/20, *Administering Oath or Declaration Remotely*

A Commissioner, etc.

Exhibit "10"

English | Français

PrICLUSIG™
Ponatinib Tablets, 15 mg and 45 mg
(as ponatinib hydrochloride)

HOME | PRESCRIBER | PHARMACIST | PATIENT

Welcome to the ICLUSIG™ Controlled Distribution Program

ICLUSIG CONTROLLED DISTRIBUTION PROGRAM (CDP)

Paladin Labs Inc. would like to inform you about the ICLUSIG Controlled Distribution Program.

This controlled distribution program has been determined by Health Canada to be required for ICLUSIG to ensure that the benefit of the drug outweighs the risks of vascular occlusion and congestive heart failure.

Only prescribers who are certified in the ICLUSIG Controlled Distribution Program can prescribe ICLUSIG.

Prescribers must read the ICLUSIG Product Monograph and the ICLUSIG Medication Guide, review the ICLUSIG Educational Slide Set, and pass the Knowledge Assessment at the end of the Slide Set.

Prescribers must review the ICLUSIG Medication Guide with patients who are initiating ICLUSIG treatment. After the review, the prescriber and the patient must sign the Patient Informed Consent Form. A signed copy of the form will be maintained by the prescriber in the patient's chart, and a signed copy will be provided to the patient.

Only pharmacies that agree to follow the ICLUSIG Controlled Distribution Program requirements will dispense ICLUSIG.

Pharmacies will only dispense an ICLUSIG prescription after verifying that the prescriber is certified in the ICLUSIG Controlled Distribution Program.

Download and Print Resources

ICLUSIG Product Monograph

ICLUSIG Medication Guide

Patient Informed Consent Form

Dear Healthcare Professional Letter (May 4, 2016)

To report SUSPECTED ADVERSE REACTIONS, contact Paladin or its designee at 1-888-867-7426 or medinfo@paladinlabs.com or Health Canada at 1-866-234-2345 or www.healthcanada.gc.ca/medeffect.

This is **Exhibit "10"** referred to in the Affidavit sworn remotely by Nick Boorman, stated as being at the City of Toronto, in the Province of Ontario, before me at the City of Toronto, in the Province of Ontario, on September 29, 2023, in accordance with O. Reg. 431/20, *Administering Oath or Declaration Remotely*

A Commissioner, etc.

Exhibit "11"

Ponatinib – US (IQVIA)

Manufacturer	Molecule	Strength	Data / Tot Dollars / Year 2022	2021	2020	Tot Ext Units 2022	2021	2020
			$	$				
TAKEDA PHARM USA	PONATINIB	10MG	3,635,889	1,279,380		5,880	2,220	
TAKEDA PHARM USA	PONATINIB	15MG	$ 140,020,386	$ 172,377,124	$ 176,846,181	228,540	310,290	402,630
TAKEDA PHARM USA	PONATINIB	30MG	$ 45,399,089	$ 16,350,828		74,100	28,350	
TAKEDA PHARM USA	PONATINIB	45MG	$ 36,911,040	$ 35,198,939	$ 29,967,272	60,270	62,970	66,750
Grand Total			**$ 225,966,404**	**$ 225,206,271**	**$ 206,813,453**	**368,790**	**403,830**	**469,380**

Ponatinib – Canada (IQVIA)

Manufacturer	Molecule	Strength	Values / Sum of Dollars Total / Calendar Year 2022	2021	2020	Sum of Dosages Total 2022	2021	2020
TAKEDA	PONATINIB	15MG	$8,210,594	$7,368,327	$5,999,626	51,900	46,860	39,240
Grand Total			**$8,210,594**	**$7,368,327**	**$5,999,626**	**51,900**	**46,860**	**39,240**

This is **Exhibit "11"** referred to in the Affidavit sworn remotely by Nick Boorman, stated as being at the City of Toronto, in the Province of Ontario, before me at the City of Toronto, in the Province of Ontario, on September 29, 2023, in accordance with O. Reg. 431/20, *Administering Oath or Declaration Remotely*

A Commissioner, ~~etc.~~

Exhibit “12”

Search Products

Below you can search for drug products that are marketed for sale in Canada. The search results will show whether there has been a shortage and/or discontinuation report for the product.

To search for shortage and discontinuation reports, please refer to the Search Reports page.

For more information on how to search products, see “How to Search” section in the Website overview for public users, found in the About & Resources page.

Search Filters ^

Keywords:

Search DIN, company name and drug name

Ingredients

ponatinib

Use "AND" to search for multiple ingredients (e.g. "iron AND vitamin b")

ATC code

ATC description

Search | Clear Filter

Brand name	Drug Identification Nu…	Company Name	Strength	Reports
ICLUSIG	02437333	TAKEDA PHARMACEU…	15MG	0

Brand name	Drug Identification Nu…	Company Name	Strength	Reports
ICLUSIG	02437341	TAKEDA PHARMACEU…	45MG	0

1

Showing 1 to 2 of 2

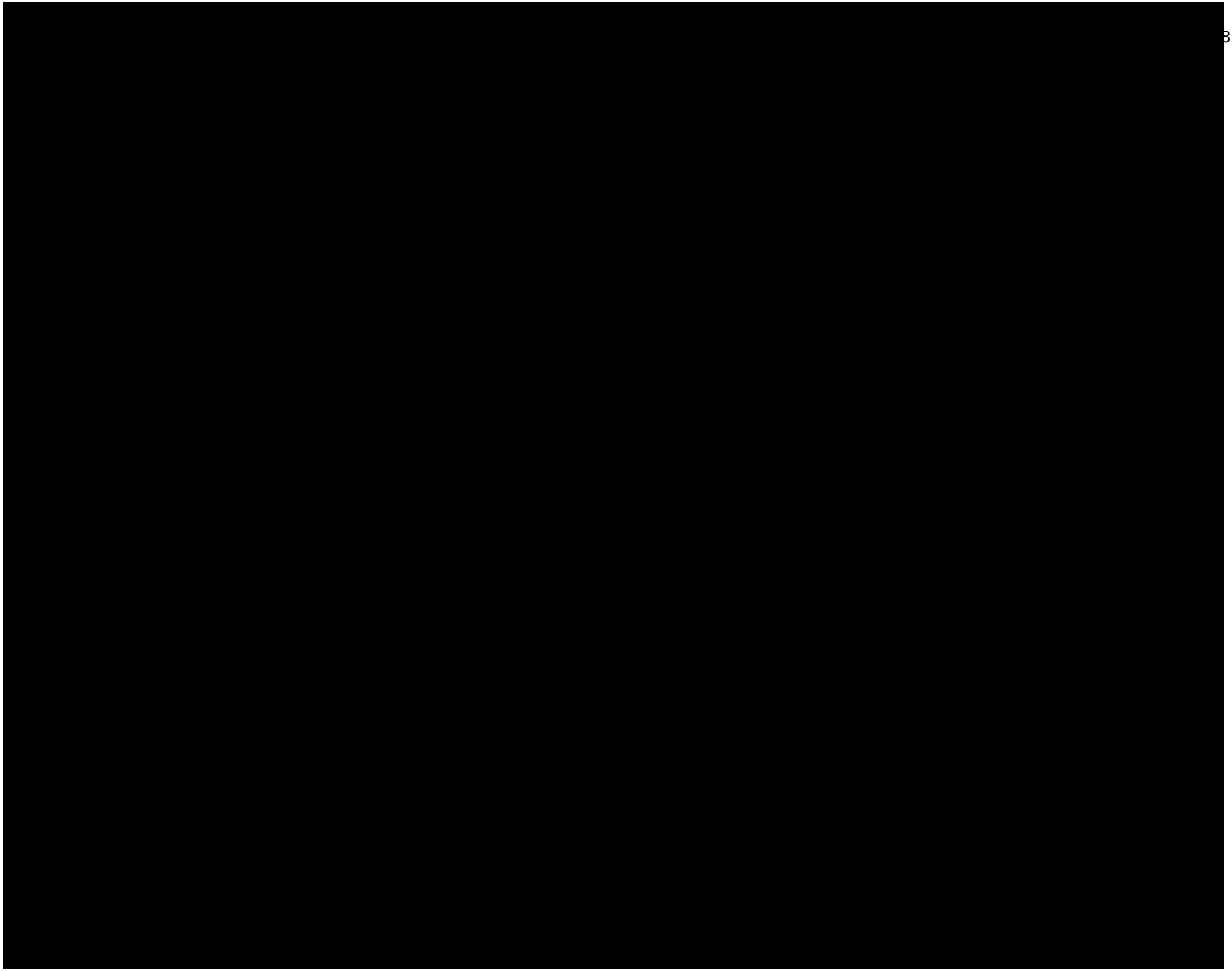
This is **Exhibit "12"** referred to in the Affidavit sworn remotely by Nick Boorman, stated as being at the City of Toronto, in the Province of Ontario, before me at the City of Toronto, in the Province of Ontario, on September 29, 2023, in accordance with O. Reg. 431/20, *Administering Oath or Declaration Remotely*

A Commissioner, etc.

Exhibit "13"

Exhibit "14"

[redacted]



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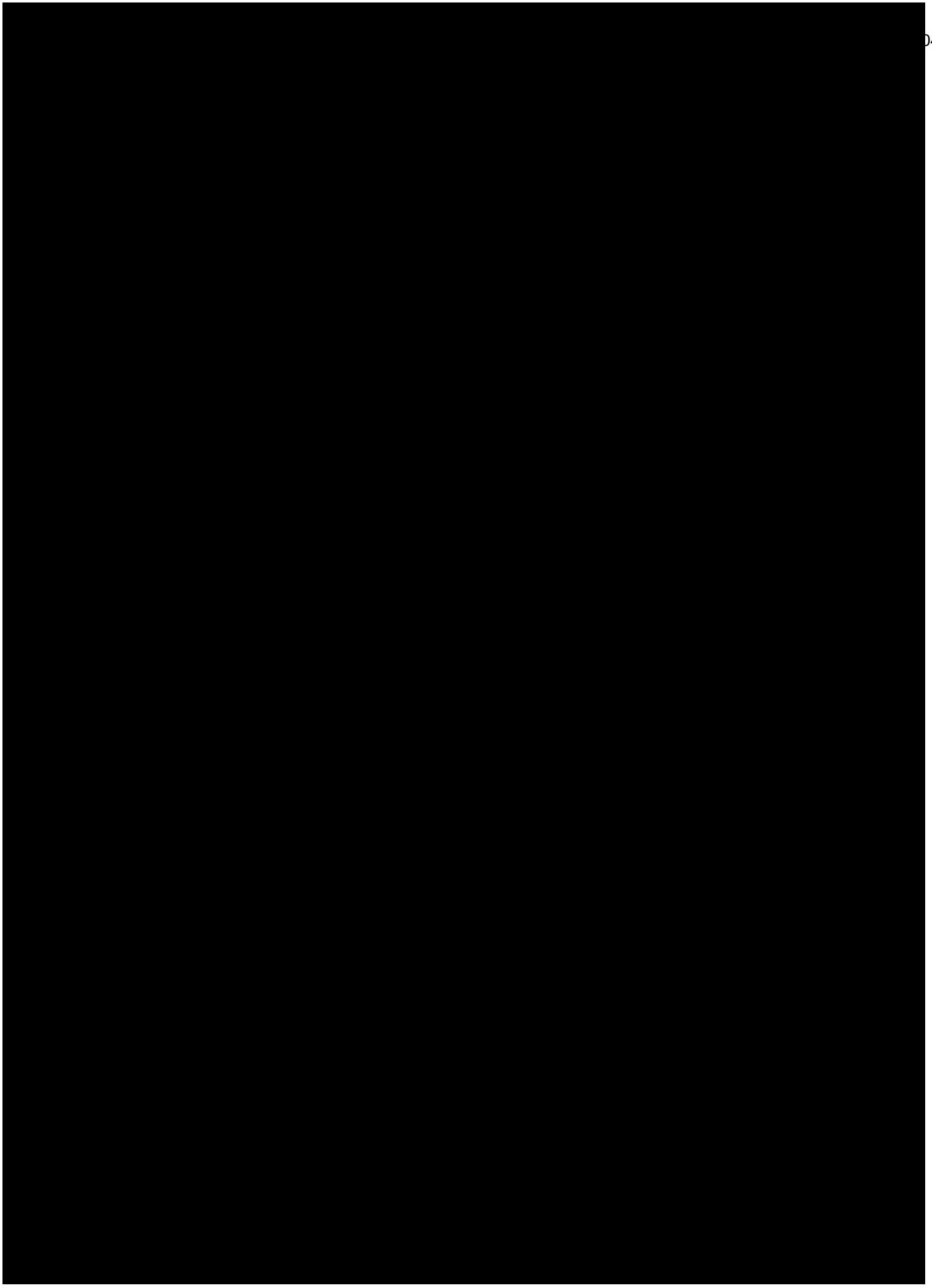

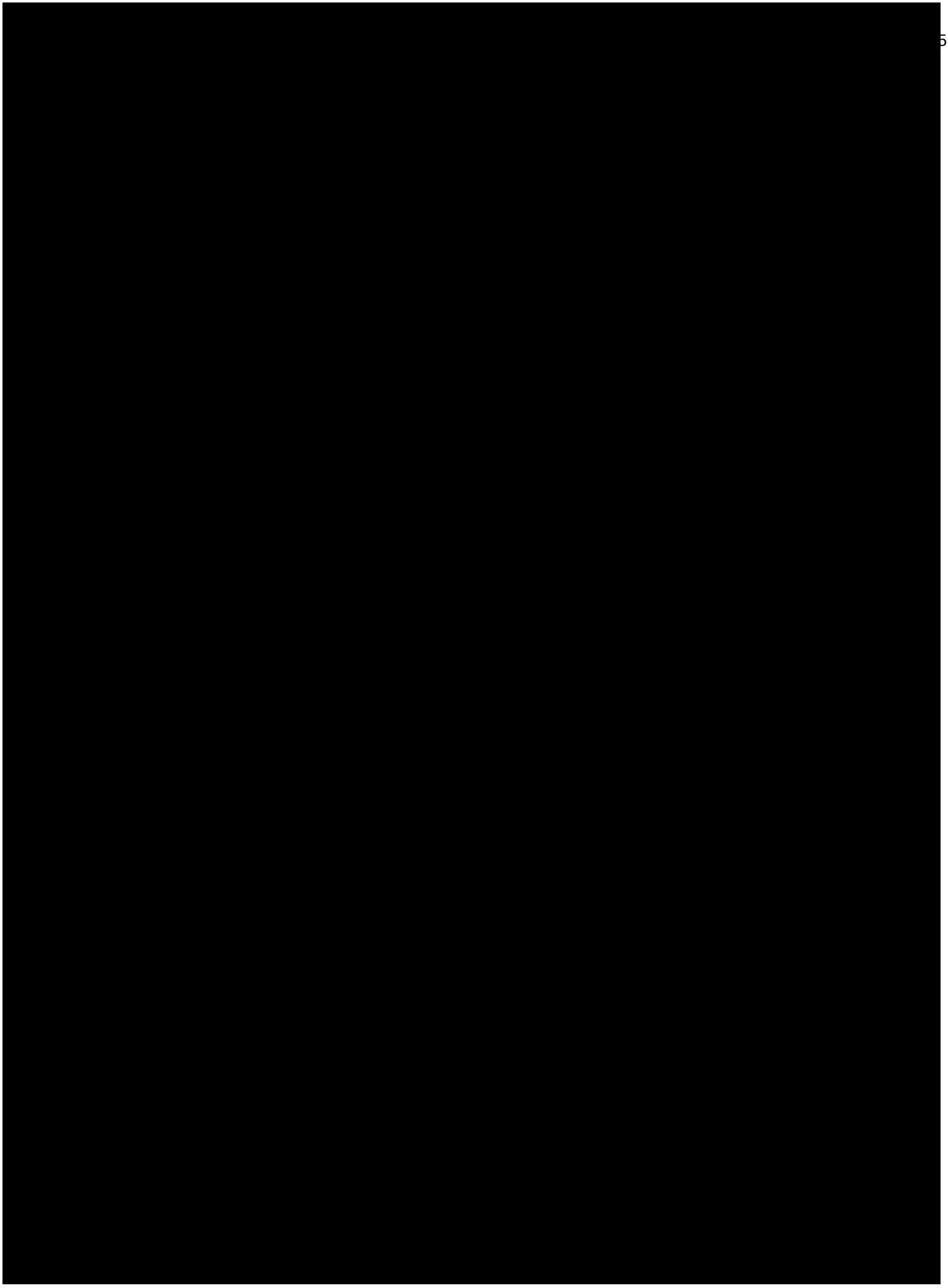

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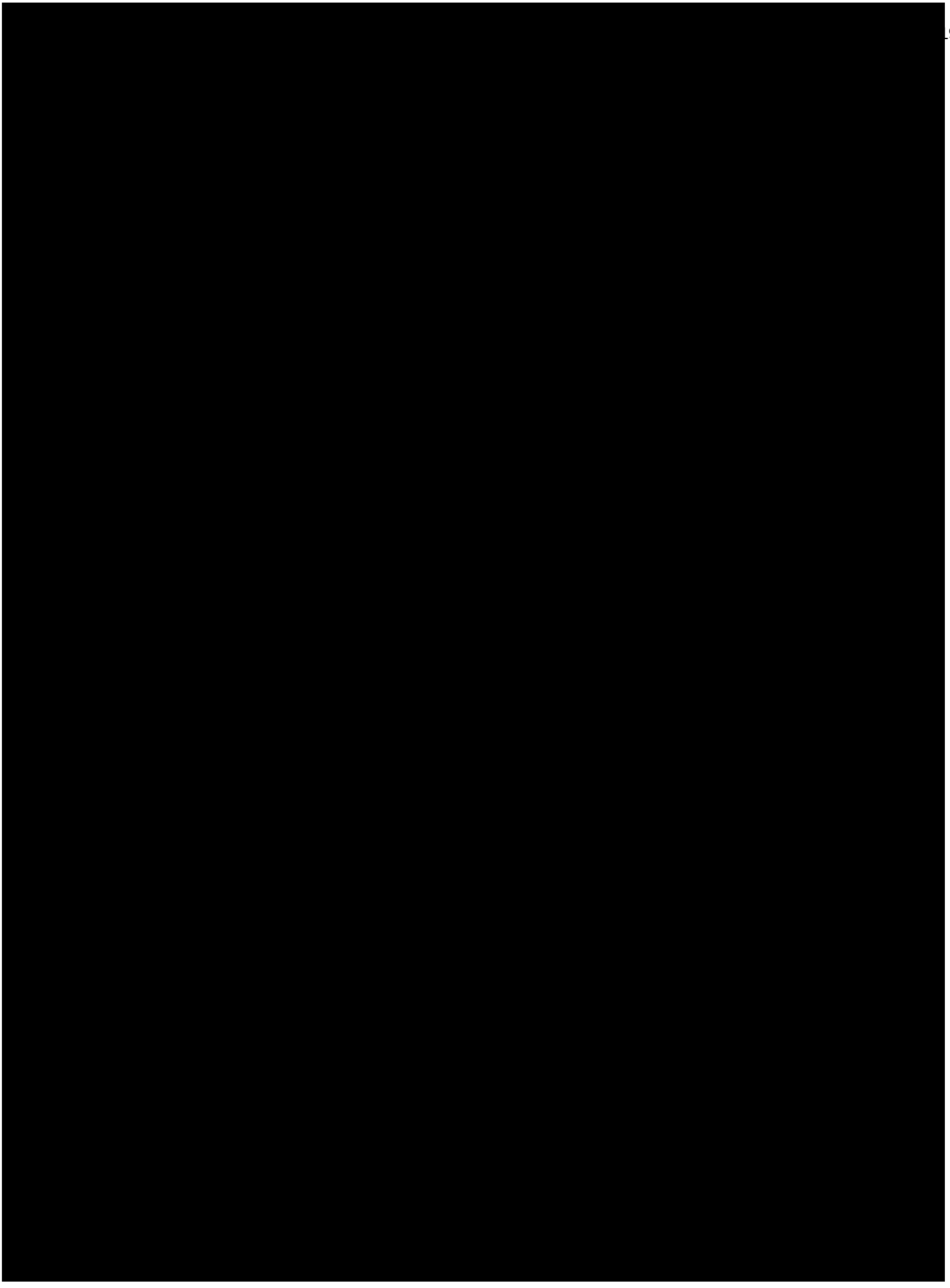

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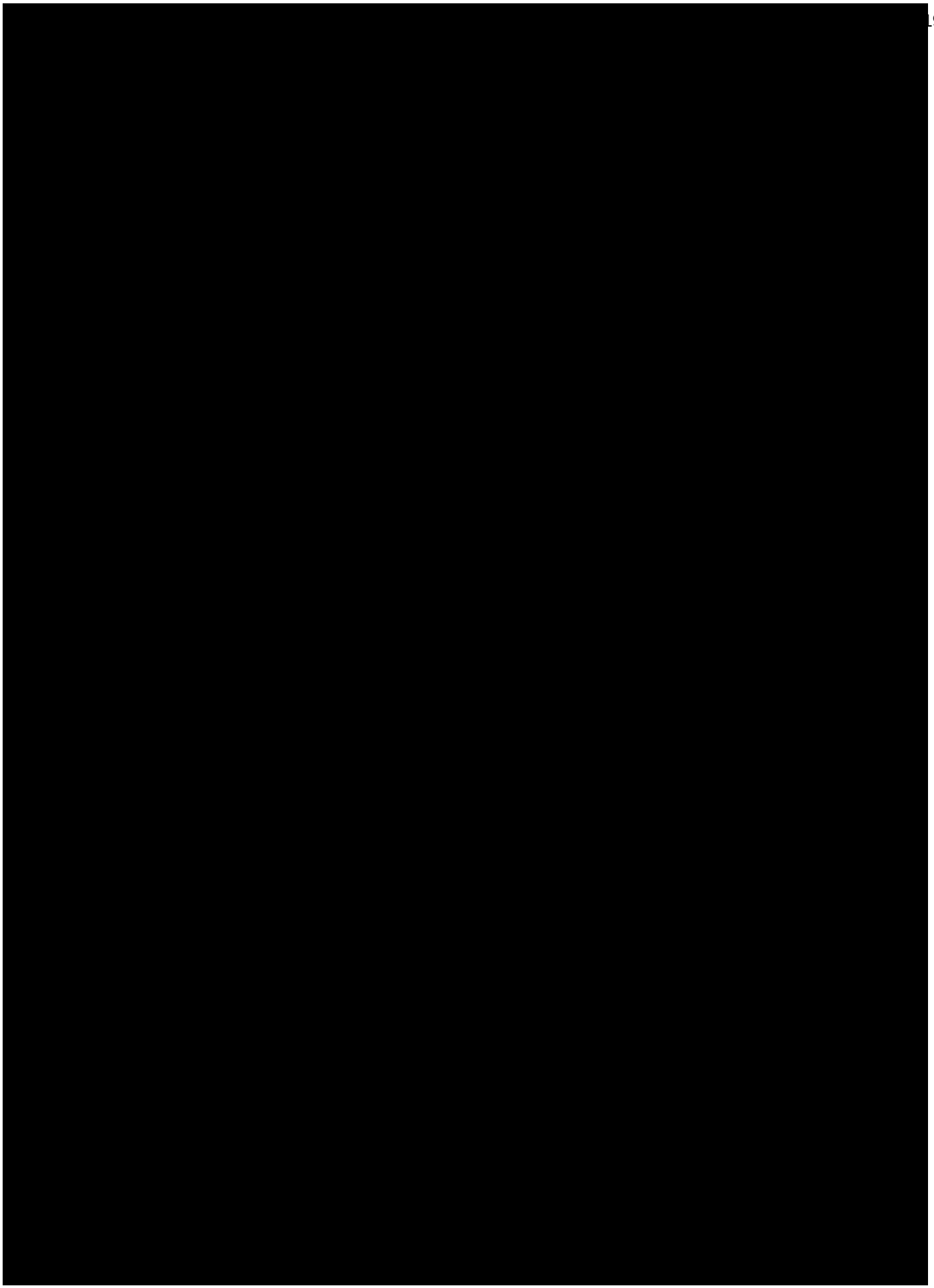

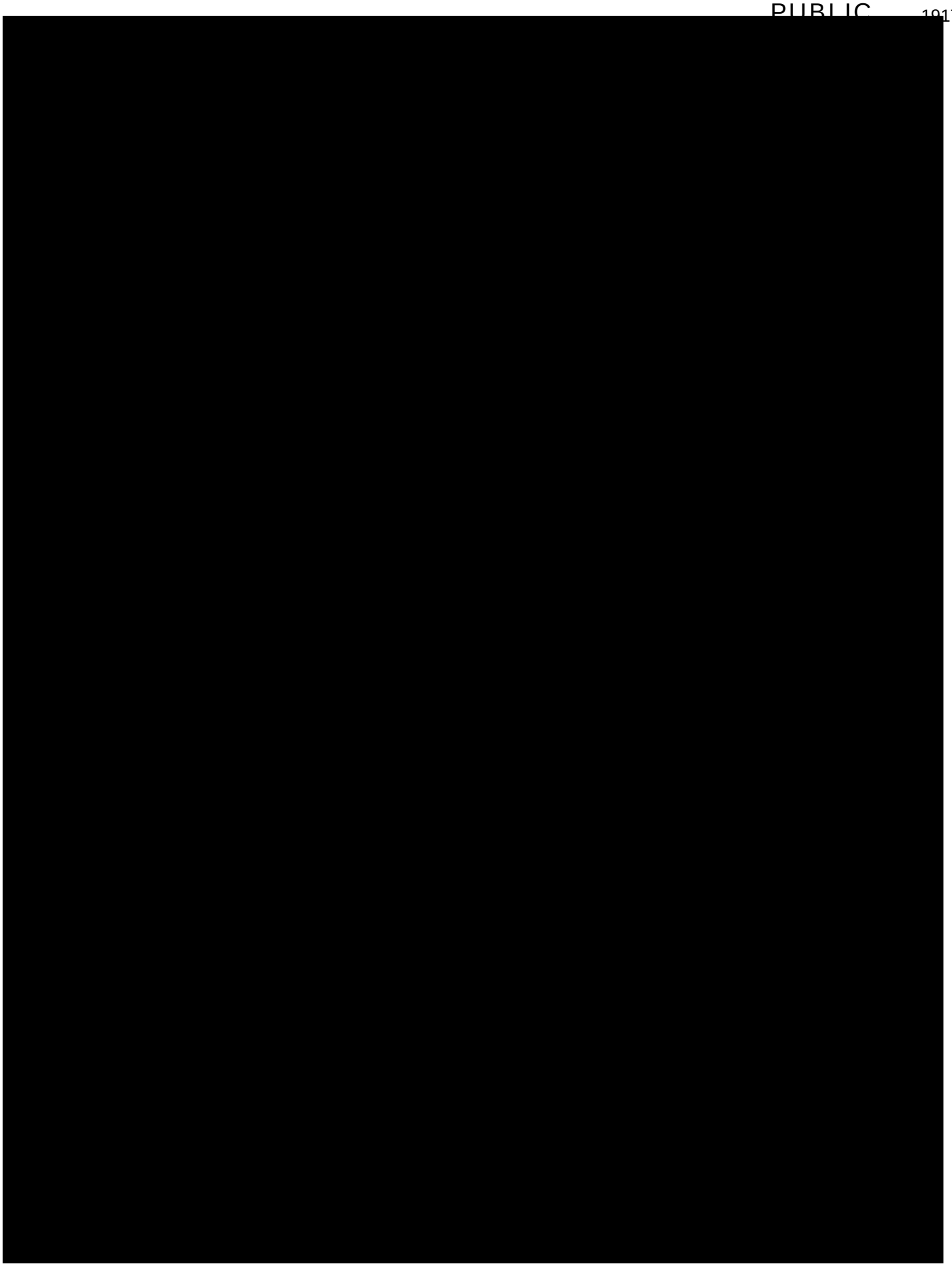

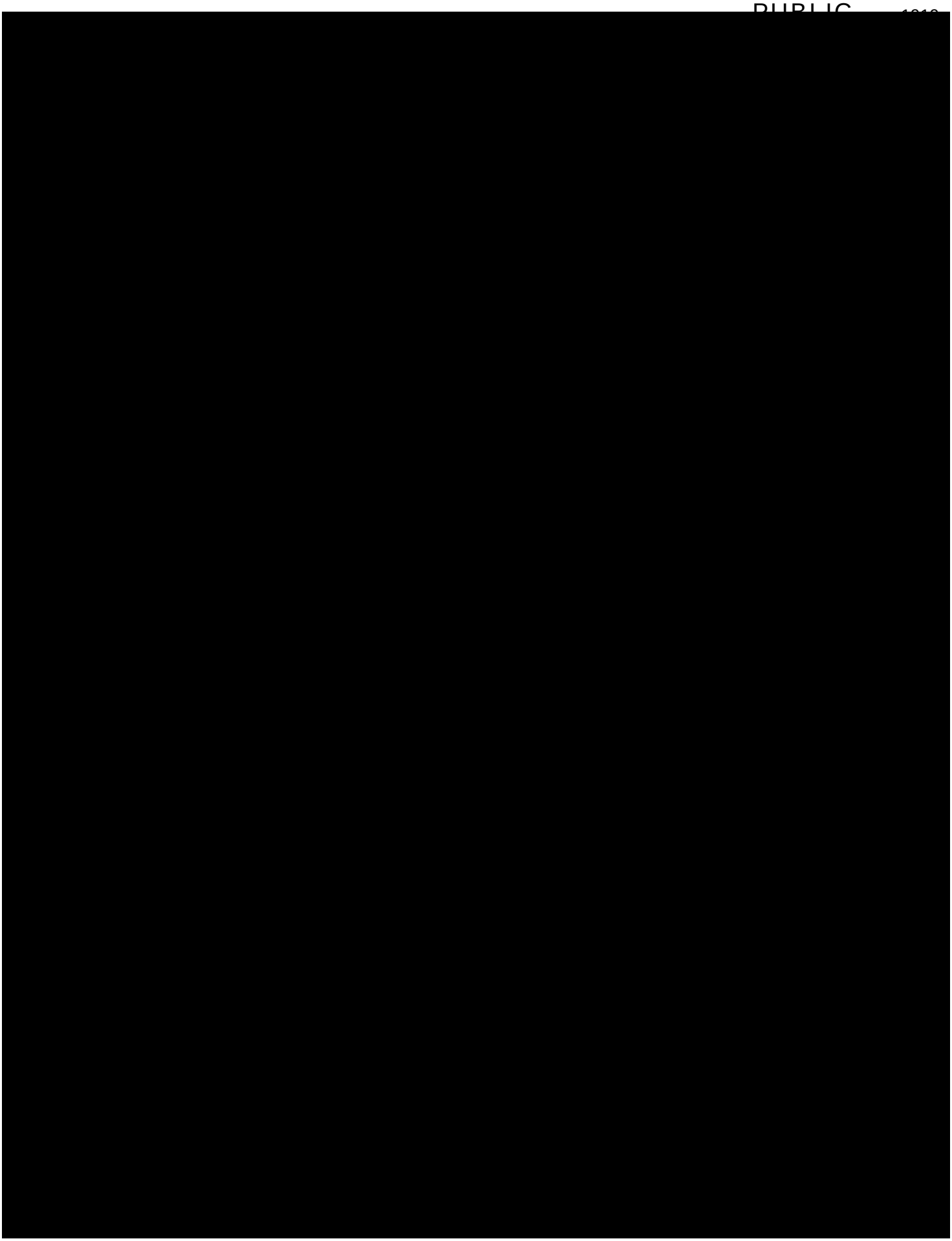

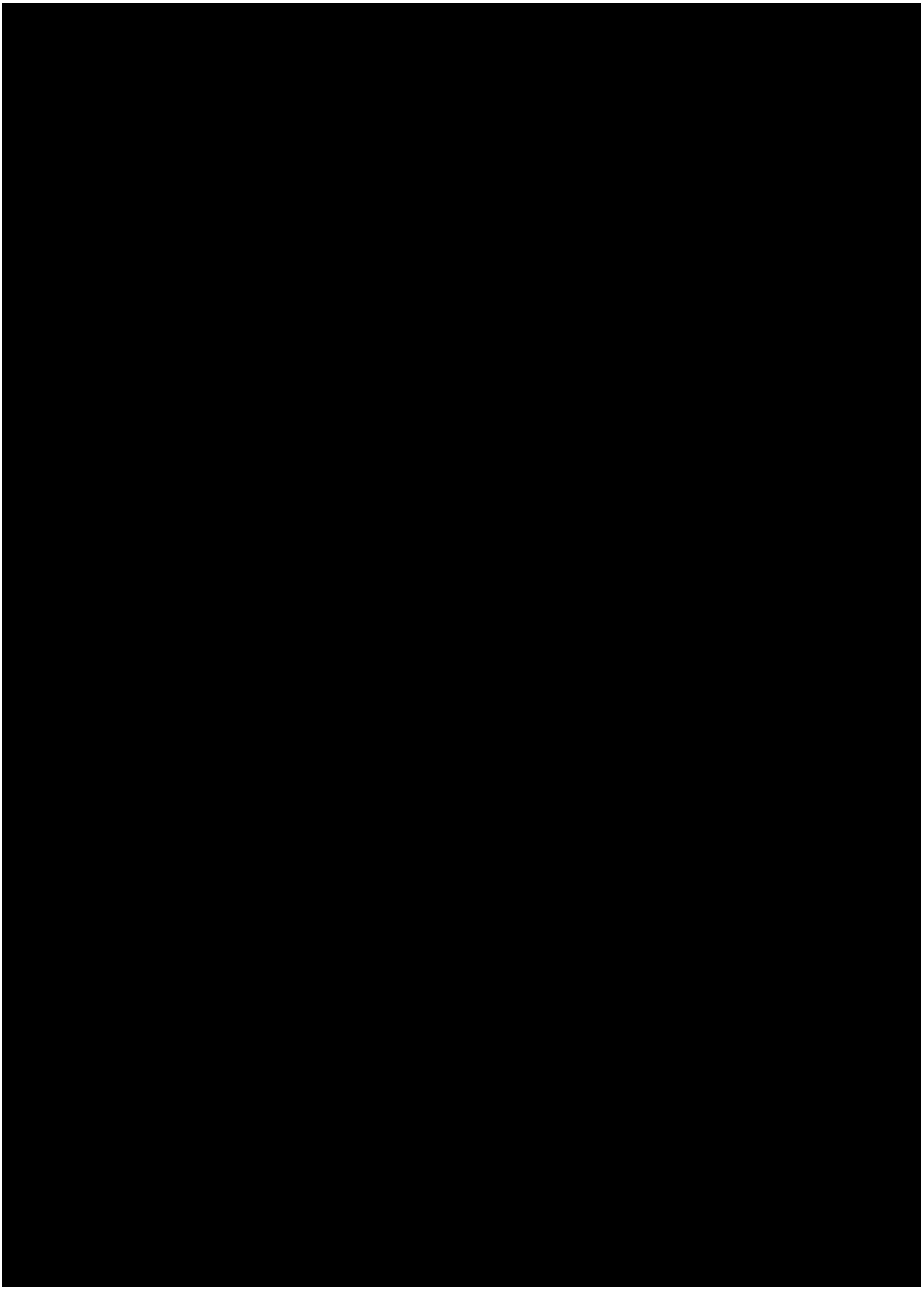

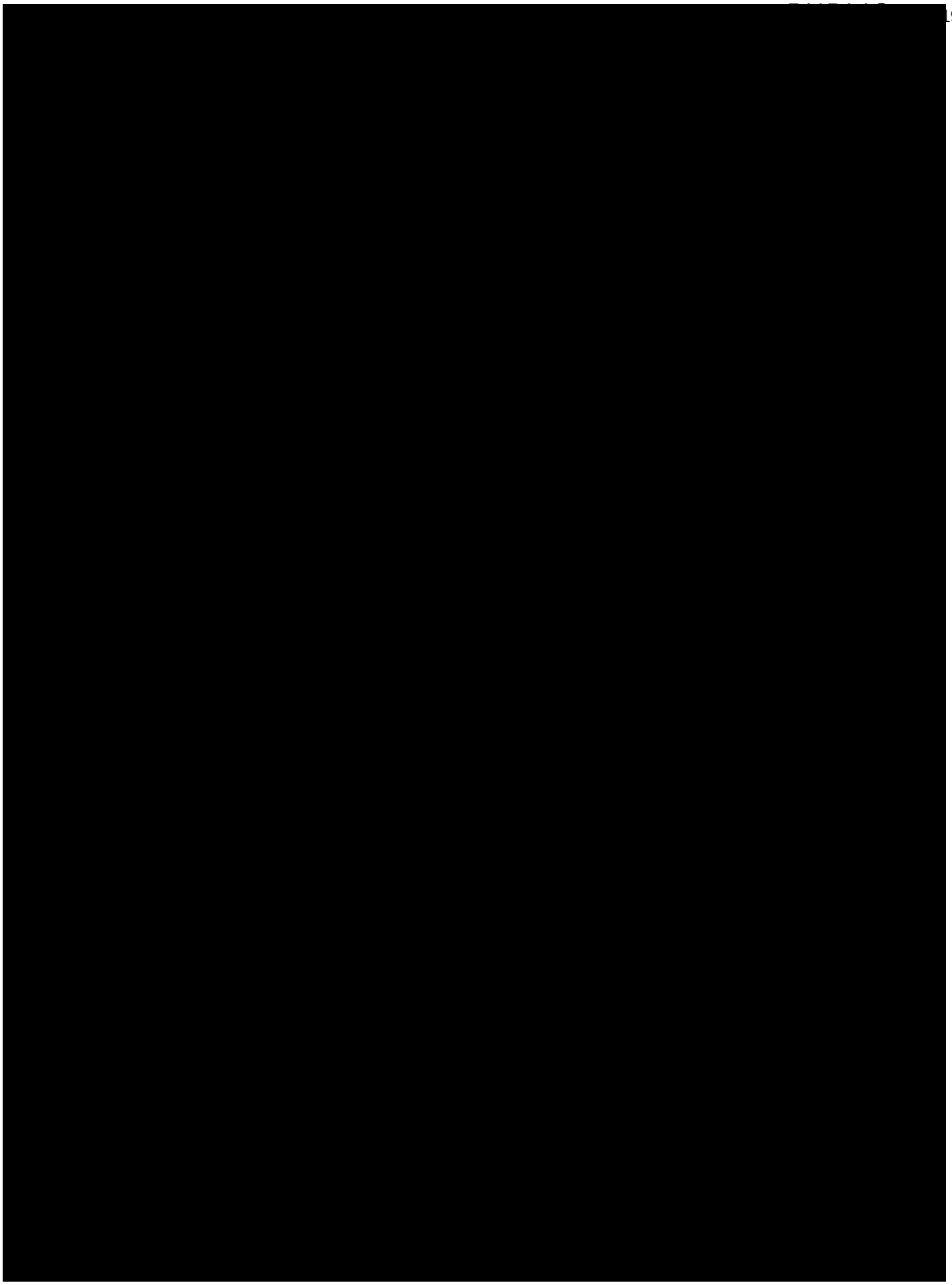

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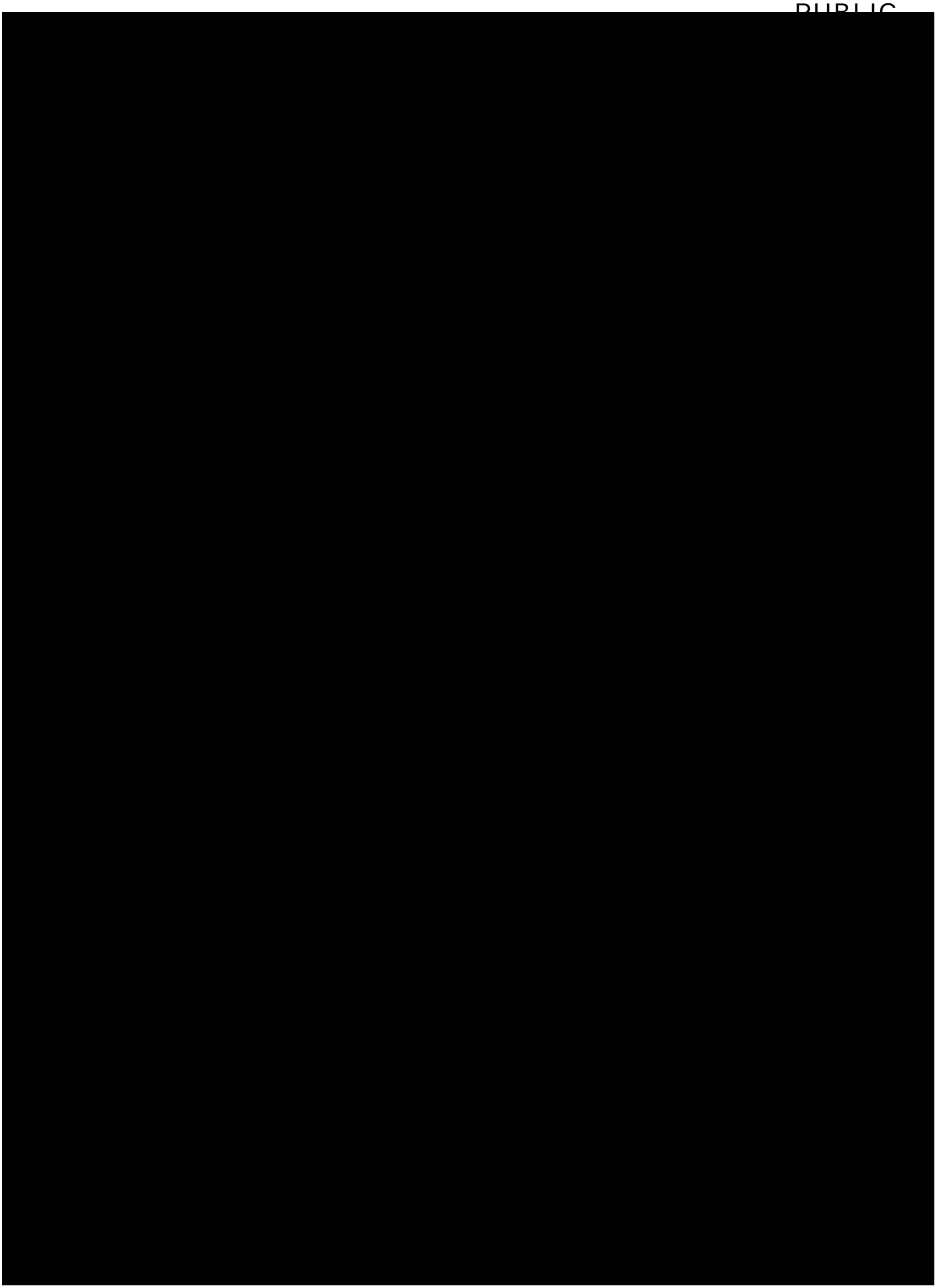

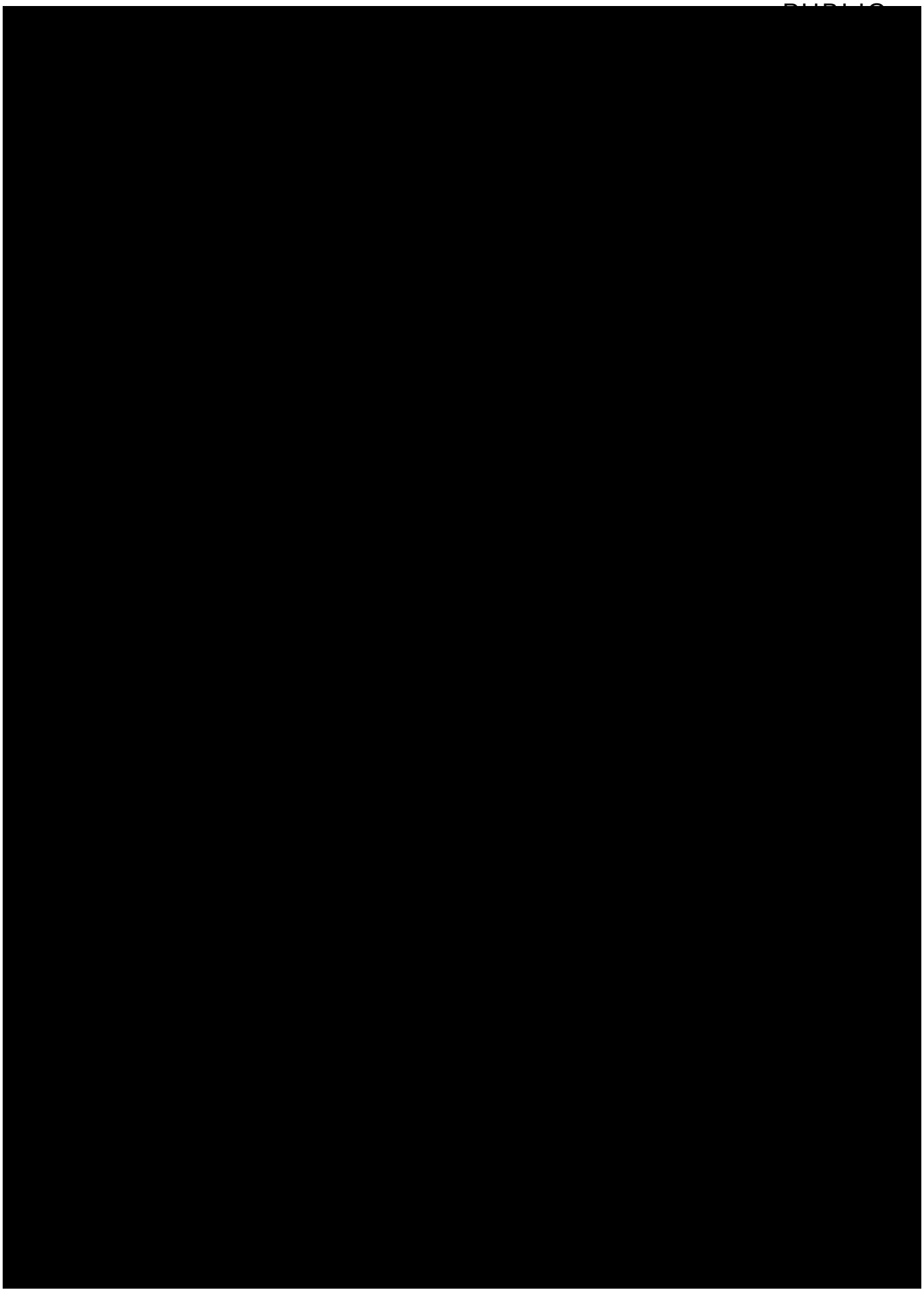

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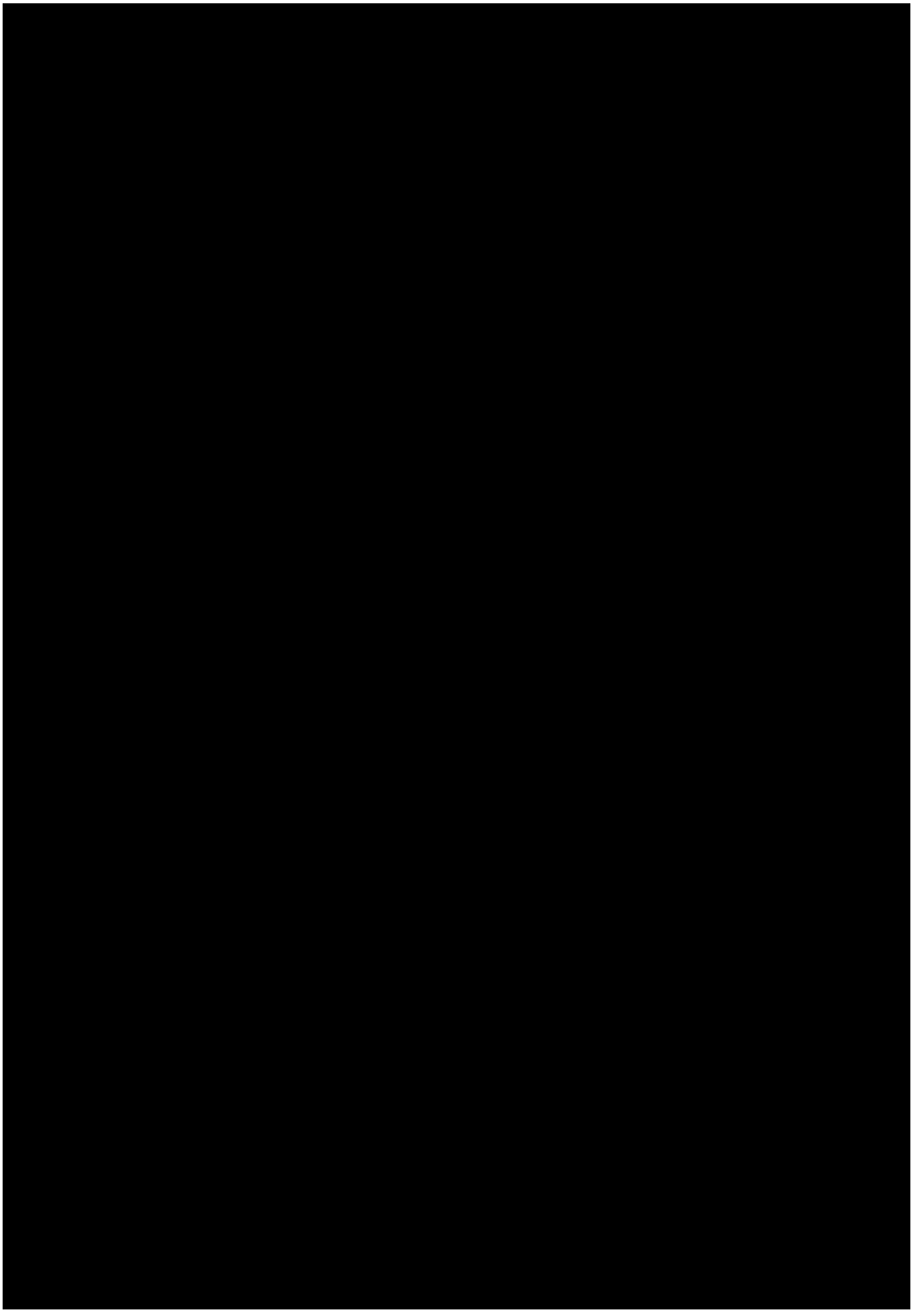

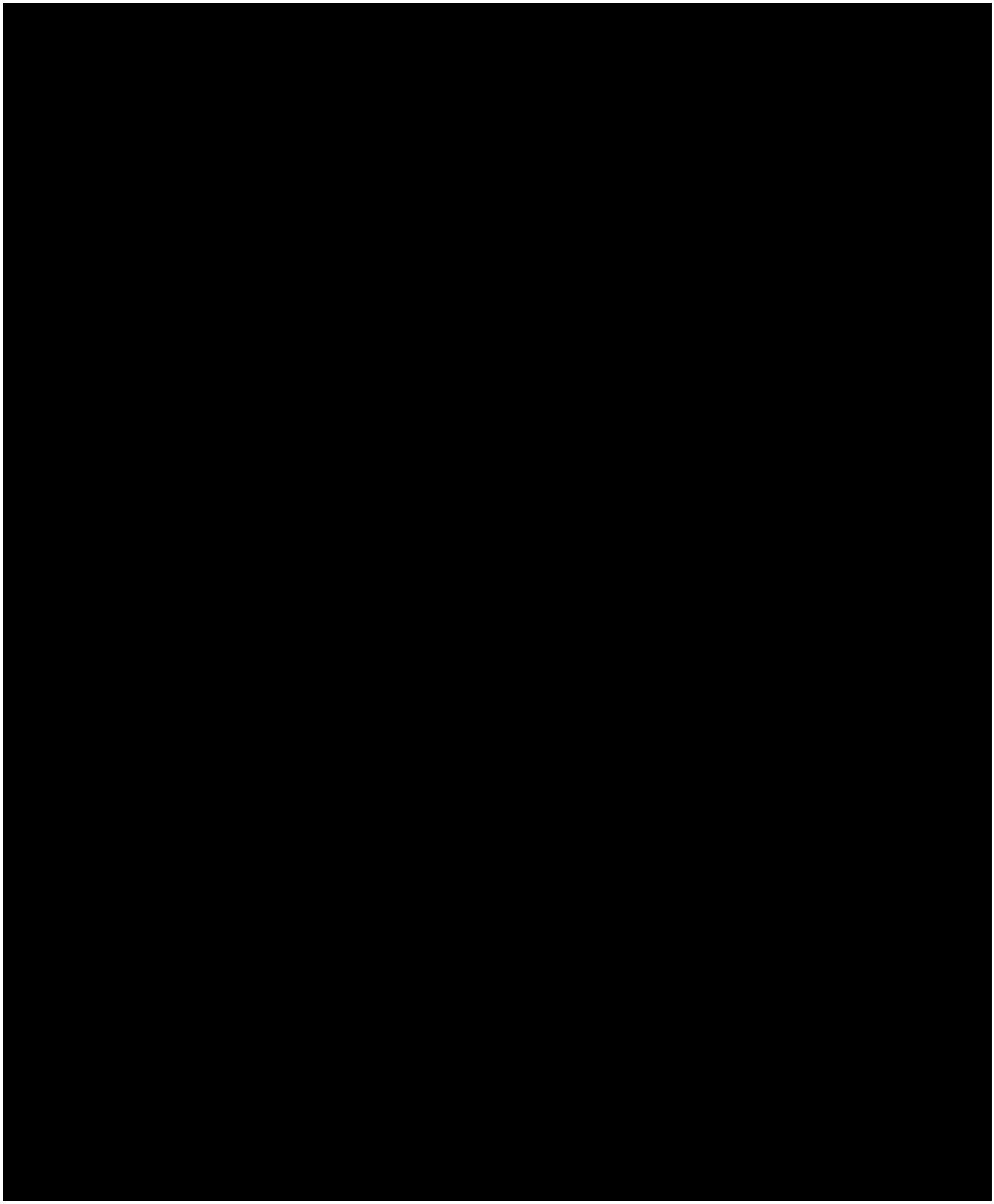

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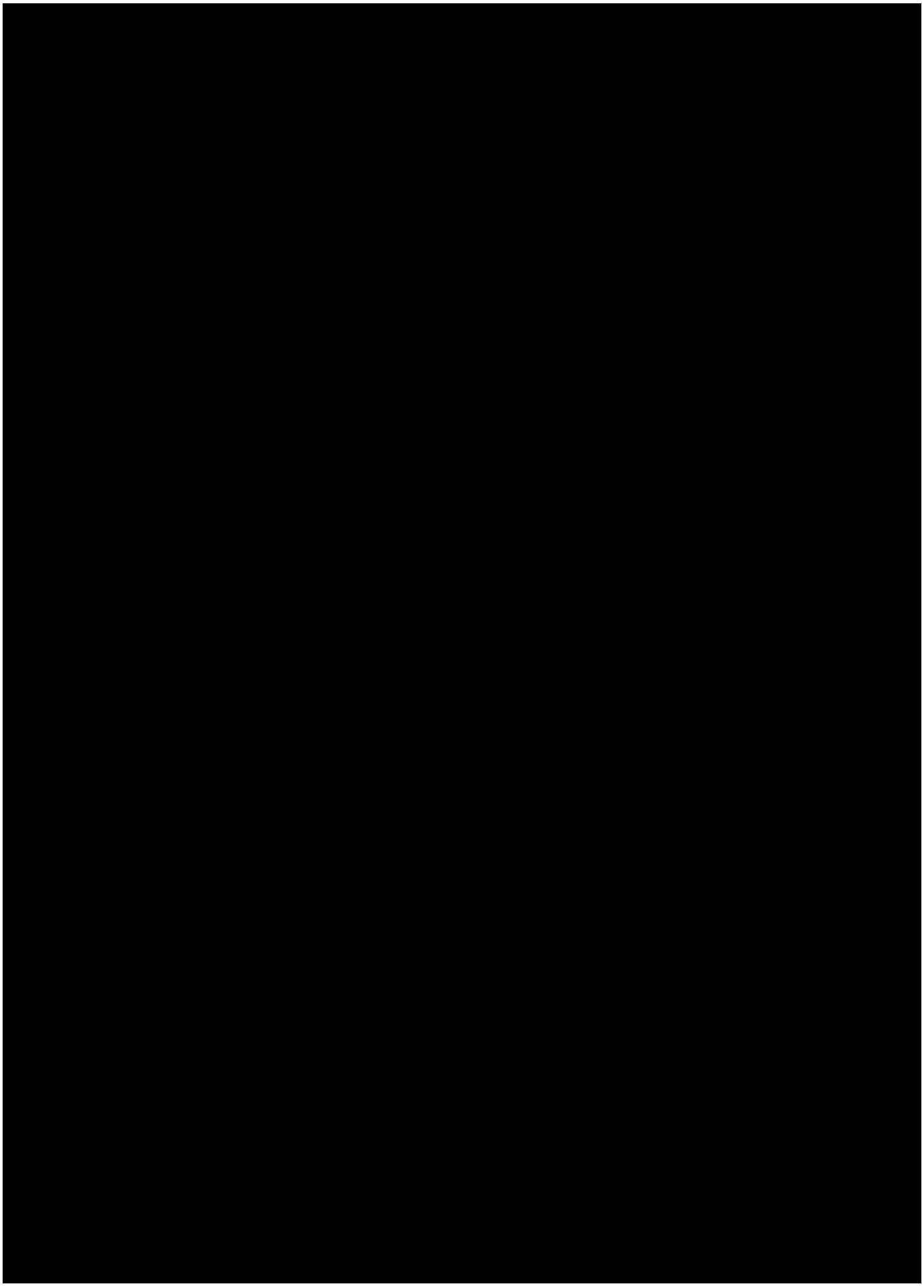

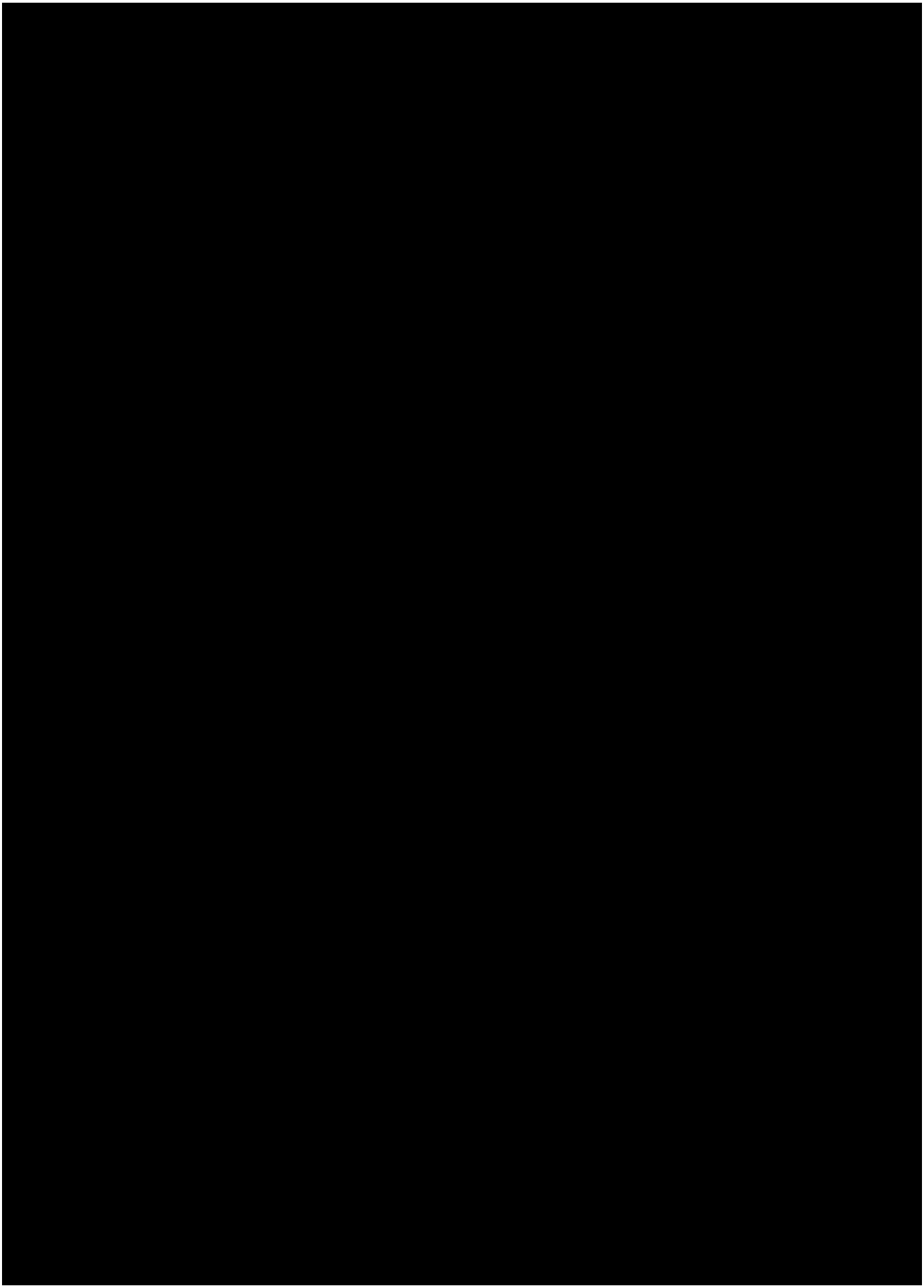

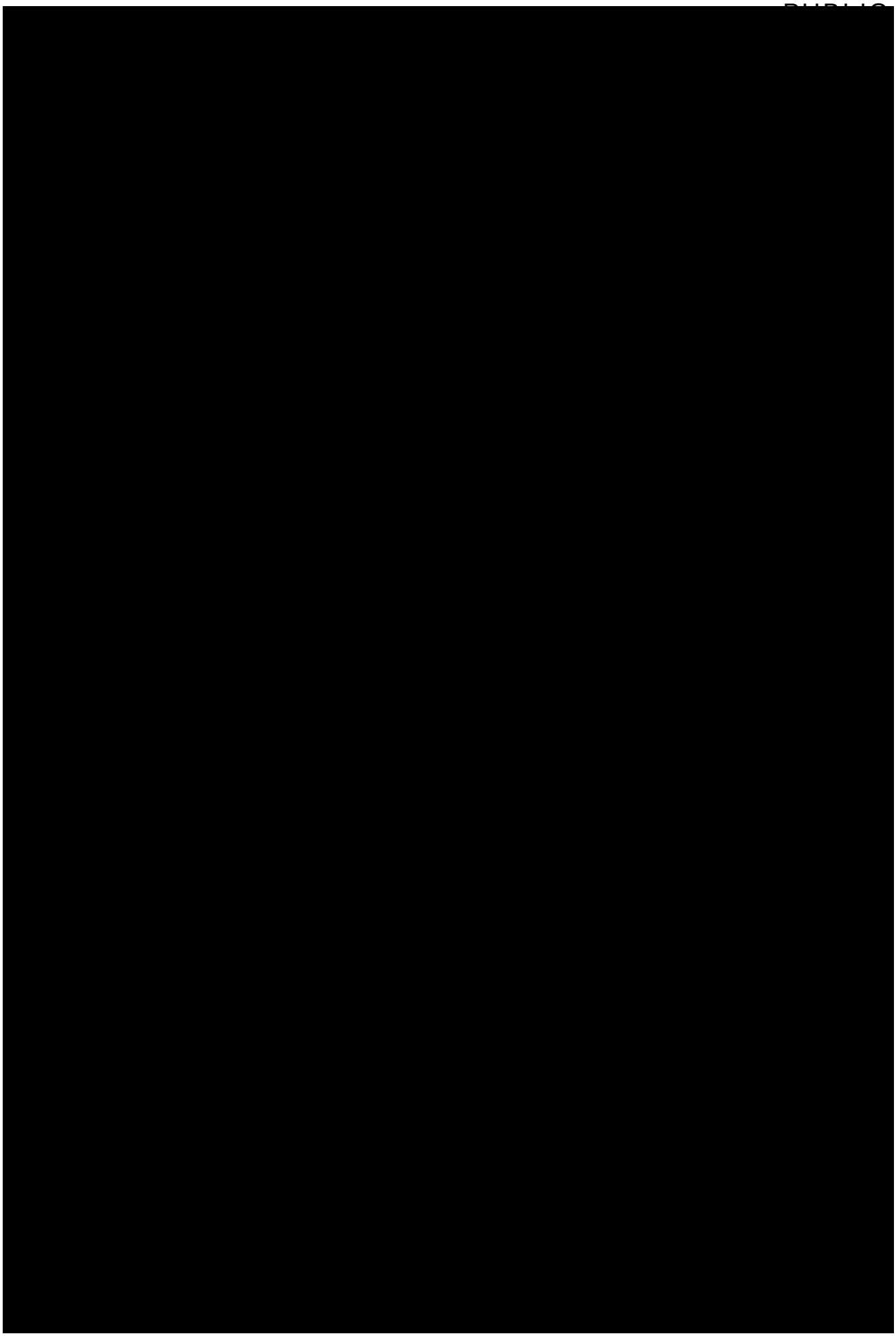

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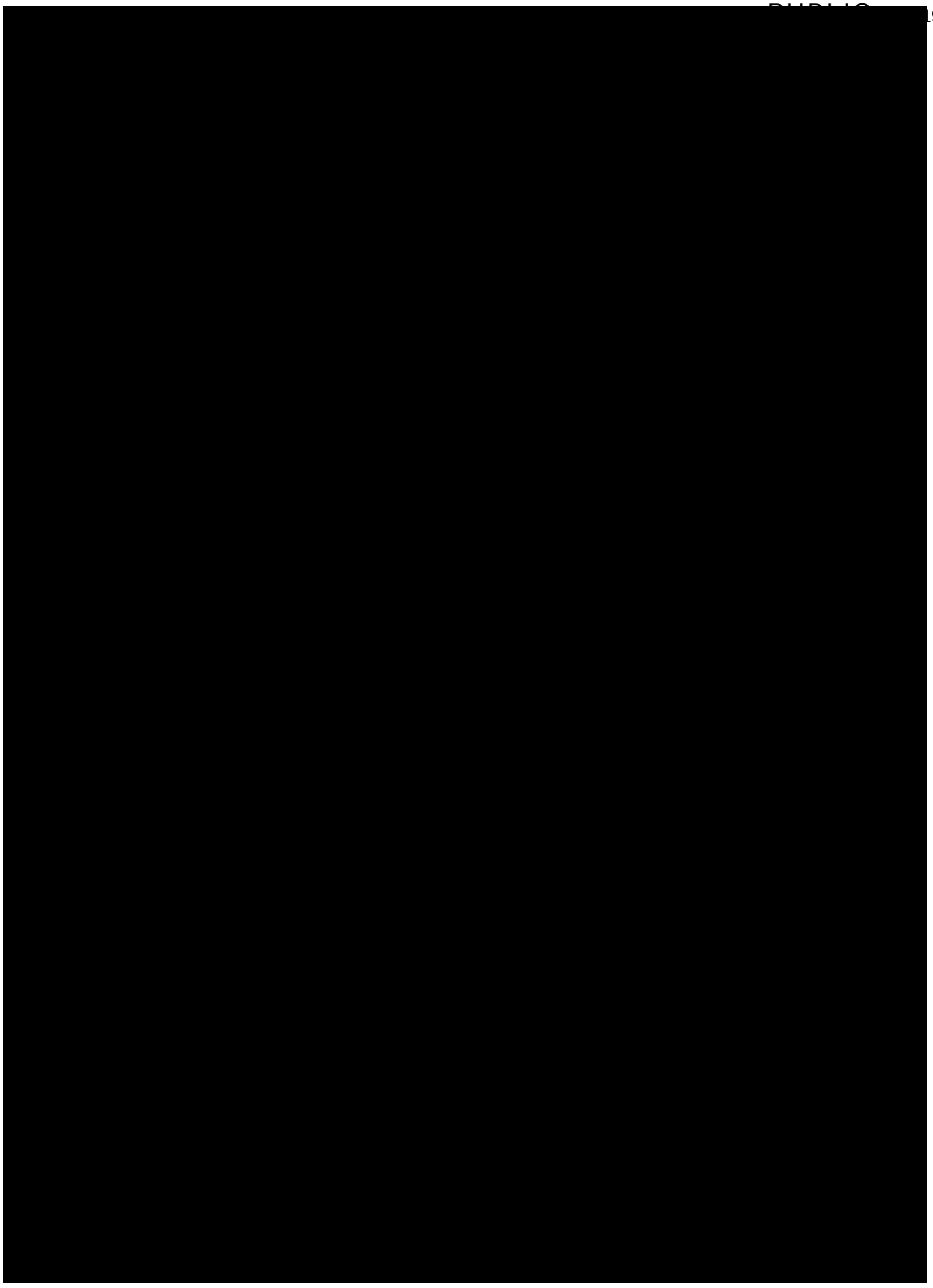

Exhibit “19”

APOTEX
Canadian-Based
Global Health Company

June 12, 2023

Via Federal Express

Attn: Legal Counsel
Takeda Pharmaceuticals U.S.A., Inc.
95 Hayden Ave.
Lexington, MA, United States 02421

Attn: Legal Counsel
Paladin Labs Inc.,
100 Alexis-Nihon Blvd #600
Saint-Laurent, QC H4M 2P2
(as Takeda's Canadian importation and distribution partner)

RE: Iclusig Tablets (Ponatinib Hydochloride) – Access to Canadian Reference Product

To Whom It May Concern:

Apotex Inc. ("Apotex") is a Canadian, global pharmaceutical company that develops and manufactures high-quality, affordable medicines (both generic and innovative pharmaceuticals) for patients in Canada and around the world.

Apotex is currently investigating whether to develop and commercialize a generic version of Iclusig® tablets 15mg and 45mg comprising ponatinib hydrochloride (DIN No's 02437333 and 02437341) in Canada.

To continue and further its investigations, Apotex will seek to ensure that its generic ponatinib hydrochloride tablets are safe and effective for Canadian consumers by demonstrating, through Bioequivalence and other required testing that its generic ponatinib hydrochloride tablets are bioequivalent to Iclusig® tablets 15mg, 45mg, manufactured by Takeda Pharmaceuticals U.S.A. ("Takeda") Inc.

Apotex has been unable to purchase Iclusig® tablets as the Canadian Reference Product (CRP) through its normal distribution channels. Apotex has been advised that supply is not permissible due to the nature of the product and the strict controls over it by Takeda. While we are unsure what this precisely means, Apotex is aware that Iclusig® is subject to a Risk Management Program ("RMP") filed with Health Canada. Apotex has created appropriate protocols for transporting, retaining and undertaking the testing noted above. More particularly, Apotex's protocol contains or will contain safety precautions that are comparable to the existing RMP for Iclusig.®

As a result, Apotex now seeks to purchase samples of the CRP directly from Takeda or Third Party designated by Takeda (packs must have at least 18 months shelf life):

- 15mg: 6 Packs of 60s (360 tablets)

Apotex is willing to pay the Manufacturers List Price for the requested quantities of Iclusig® and will use the tablets solely for the purposes of conducting bioequivalence testing and/or to generate data to support the filing of its planned Abbreviated New Drug Submission referencing Iclusig®. The tablets will not be intended for commercial sale and will not be resold.

Sharon Kovacs, Associate Director, Project Management, will be the Apotex point of contact for communications and receipt of the Iclusig® product and such product should be sent to:

Apotex Inc.,
150 Signet Drive, Toronto
ON M9L 1T9
CANADA.

As you are surely aware, elements of an RMP, such as controlled distribution programs, cannot restrict access to CRPs for generic drug manufacturers that are conducting the required regulatory testing. *See* Health Canada's August 13, 2020 "Notice of clarification to drug manufacturers and sponsors - Risk Management Plans – Update," available at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/notice-clarification-drug-manufacturers-sponsors-risk-management-plans.html.

We reserve all rights under Canadian law including under the *Competition Act.*

We request that you reply to this letter via e-mail (ojabri@apotex.com) within 5 business days.

We look forward to hearing from you.

Yours very truly,
Apotex Inc.

DocuSigned by:
3CB33B389BBA4FA...

Omar Jabri
Assistant General Counsel, IP
ojabri@apotex.com

This is **Exhibit "19"** referred to in the Affidavit sworn remotely by Nick Boorman, stated as being at the City of Toronto, in the Province of Ontario, before me at the City of Toronto, in the Province of Ontario, on September 29, 2023, in accordance with O. Reg. 431/20, *Administering Oath or Declaration Remotely*

A Commissioner, etc.

Exhibit “20”

APOTEX
Canadian-Based
Global Health Company

Adam Rambert
Direct Dial: (416) 401-7334
E-mail: arambert@apotex.com

August 24, 2023

VIA E-MAIL
AND COURIER

Takeda Canada
Bay Adelaide Centre
22 Adelaide Street West
Suite 3800
Toronto, Ontario
M5H 4E3
Canada

Attention: **Rute Fernandes**
General Manager of Canada

Takeda Canada
Bay Adelaide Centre
22 Adelaide Street West
Suite 3800
Toronto, Ontario
M5H 4E3
Canada

Attention: **Matthew Catellarin**
Head of Legal, Canada

Paladin Labs Inc.
100 Alexis-Nihon Blvd
#600
Saint-Laurent, Quebec
H4M 2P2
Canada

Attention: **Livio Di Francesco**
Vice President & General Manager

Paladin Labs Inc.
100 Alexis-Nihon Blvd
#600
Saint-Laurent, Quebec
H4M 2P2
Canada

Attention: **Jason Lam**
Director, Government Affairs and Market Access

Endo Pharmaceuticals Inc.
1400 Atwater Drive
Malvern, PA
19355
United States

Attention: **Matthew Maletta**
Executive Vice President, Chief Legal Officer and Company Secretary

…2/

Dear Sirs and Mesdames:

Re: RE: Iclusig Tablets (Ponatinib Hydochloride) – Access to Canadian Reference Product – Letter #2

We refer to our letter dated June 12, 2023, requesting the prompt supply of certain Iclusig® tablets to Apotex Inc. ("Apotex"), which Apotex intends to utilize in connection with its efforts to demonstrate that its own ponatinib hydrochloride tablets are bioequivalent to Iclusig® and to launch a generic version of Iclusig®. A copy of that letter is enclosed. We have not received any response to our June 12 letter or its requests.

We are writing to repeat the requests in our June 12 letter.

So as not to delay any further Apotex's efforts to develop and launch a generic version of Iclusig®, we require a response to this letter within 5 business days, and for the requested supply of Iclusig® to be delivered to Apotex within 20 business days of this letter.

20 business days from the date of this letter is sufficient time to settle all reasonable supply and other terms, and to deliver the product. Apotex is prepared to work quickly in cooperation with you to permit delivery within this time frame. Accordingly, in your initial reply to this letter, please include (i) the standard supply terms that apply to the supply of a small volume of Iclusig® to an experienced generic pharmaceutical company such as Apotex, (ii) the desired pricing terms for the requested supply of Iclusig®, (iii) the payment terms and instructions (e.g., wire transfer instructions), (iv) if delivery will not be made to Apotex's offices as requested in the June 12 letter, any relevant information about the manner and place of delivery of the requested supply of Iclusig® (so that Apotex may make appropriate arrangements) and (v) any other commercially reasonable matters. Apotex is prepared to agree to reasonable commercial terms for the supply of a small amount of reference product. However, unreasonable requests that are not commercially practicable, but that are instead intended to delay the supply of the requested product, will not be honoured.

Health Canada and the Canadian Competition Bureau have each explained the importance of generic pharmaceutical companies being able to obtain prompt access to reference products for comparative testing purposes. Both agencies have also explained that Risk Management Plans and other aspects of the regulation of pharmaceutical products should not delay the supply of drugs. If the small amount of Iclusig® that Apotex has requested is not supplied promptly, or if unreasonable demands are made of Apotex that are intended to delay the supply of Iclusig®, Apotex will report such conduct to those agencies.

You may contact me via email at arambert@apotex.com at your convenience. We look forward to hearing from you.

APOTEX INC.

DocuSigned by:
Adam Rambert
CB0964175EC8440...

Adam Rambert
Assistant General Counsel,
Canada & ROW

AR/ph

This is **Exhibit "20"** referred to in the Affidavit sworn remotely by Nick Boorman, stated as being at the City of Toronto, in the Province of Ontario, before me at the City of Toronto, in the Province of Ontario, on September 29, 2023, in accordance with O. Reg. 431/20, *Administering Oath or Declaration Remotely*

A Commissioner, etc.

Exhibit “21”

From: Nikas, Alex <Nikas.Alexander@endo.com>
Sent: Friday, September 8, 2023 9:50 AM
To: Adam Rambert <arambert@apotex.com>
Cc: Katharine Weekes <kweekes@apotex.com>; Trempe, Isabelle <Trempe.Isabelle@endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>; "Matthew Castellarin" <matthew.castellarin@takeda.com>; heather.eck@takeda.com
Subject: iClusig (Ponatinib Hydrochloride) supply in Canada

Dear Mr. Rambert,

I am an attorney with Endo Pharmaceuticals, a US affiliate of Paladin Labs, distributor of iClusig (Ponatinib Hydrochloride) in Canada. We are in receipt of your correspondence of August 24, 2023. We have conferred with our US and Canadian colleagues at Takeda and determined that the most expeditious way for Apotex to procure supply of iClusig in Canada is to set up an account and place an order through Paladin Labs Customer Service Department. The contact information is below. Should you encounter any difficulties please contact us and we will work to resolve them.

Paladin Toll Free: 1-866-340-1112
Paladin Fax: 1-866-340-7221
Email: customerservicepaladin@paladinlabs.com

Regards,

Alex

Alexander A. Nikas
VP & AGC Global Commercial Ops and R&D

office 484-216-6736
mobile **445-787-2351**
Nikas.Alexander@endo.com

Endo
1400 Atwater Drive
Malvern, PA 19355

endo.com

This is **Exhibit "21"** referred to in the Affidavit sworn remotely by Nick Boorman, stated as being at the City of Toronto, in the Province of Ontario, before me at the City of Toronto, in the Province of Ontario, on September 29, 2023, in accordance with O. Reg. 431/20, *Administering Oath or Declaration Remotely*

A Commissioner, etc.

Exhibit “22”

From: Trempe, Isabelle <Trempe.Isabelle@endo.com>
Sent: Sunday, September 17, 2023 8:49 PM
To: Adam Rambert <arambert@apotex.com>; Paladin - Customer Service <customerservicepaladin@paladin-labs.com>
Cc: Nikas, Alex <Nikas.Alexander@endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>; matthew.castellarin@takeda.com; heather.eck@takeda.com; Di Francesco, Livio <DiFrancesco.Livio@Endo.com>; Katharine Weekes <kweekes@apotex.com>; De Serres, Jean <DeSerres.Jean@Endo.com>
Subject: RE: [EXTERNAL] RE: Establish new account for Apotex, and order for ICLUSIG

> **Caution:** This is an external email. Please take care when clicking links or opening attachments. When in doubt, contact the Global Service Desk.

Dear Adam, We have less than 2 months of stock and cannot jeopardize the patient continuity of stock with this rather large volume request. We will let you know when we receive and release next lot which is expected in the next month. We also asked (Jean De Serres email) confirmation of use: for human or not. We need this to be answered since the product is on CDP and we need to certify prescriber and pharmacist before shipping if for use by humans.

Kind regards, isabelle

Vice-présidente, Opérations commerciales / Accès aux marchés -
Vice President, Commercial Operations / Market Access
100 Boul. Alexis-Nihon, Bureau/Suite 600 Montréal, QC, H4M 2P2 Canada
trempe.isabelle@endo.com
www.paladinlabs.com

From: Adam Rambert <arambert@apotex.com>
Sent: Friday, September 15, 2023 12:25 PM
To: Paladin - Customer Service <customerservicepaladin@paladin-labs.com>
Cc: Nikas, Alex <Nikas.Alexander@endo.com>; Trempe, Isabelle <Trempe.Isabelle@endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>; matthew.castellarin@takeda.com; heather.eck@takeda.com; Di Francesco, Livio <DiFrancesco.Livio@Endo.com>; Lam, Jason <Lam.Jason@endo.com>; Katharine Weekes <kweekes@apotex.com>
Subject: [EXTERNAL] RE: Establish new account for Apotex, and order for ICLUSIG

Dear Paladin Labs – I'm following from my email of September 8, below. As noted, we require the supply of this drug very promptly. What can we do to expedite this transaction? Thanks in advance for your quick reply.

@Alex Nikas – Please let us know ASAP if there is another person or email address at Paladin Labs whom we should contact for this order, or if there is any other reason why the order we have requested has not been fulfilled promptly.

Regards,

Adam Rambert
Assistant General Counsel

Apotex
150 Signet Drive, Toronto, ON M9L 1T9
T: 416-401-7334 | M: 647-532-8174 | arambert@apotex.com | www.apotex.com

---

From: Adam Rambert
Sent: Friday, September 8, 2023 2:47 PM
To: customerservicepaladin@paladinlabs.com
Cc: nikas.alexander@endo.com; trempe.isabelle@endo.com; kennedy.kristin@endo.com; matthew.castellarin@takeda.com; heather.eck@takeda.com; difrancesco.livio@endo.com; lam.jason@endo.com; Katharine Weekes <kweekes@apotex.com>
Subject: Establish new account for Apotex, and order for ICLUSIG

Dear Paladin Labs,

On August 24, we wrote to Paladin Labs (and Takeda and Endo) to request the supply of 6 packs of 60 15 mg tablets of ICLUSIG (ponatinib hydrochloride) – in other words, 360 15 mg tablets. See the attached correspondence.

Per the email below, Endo and Takeda have instructed Apotex to contact you to establish an account and place the requested order. Please set out the information you require to establish an account in the name of Apotex Inc. As noted in our August 24 letter, we require the supply of this product very promptly, and therefore your cooperation to establish our account and fulfill our order is much appreciated. We understand that ICLUSIG is subject to a Risk Management Plan; as your counsel will advise you, that plan should not delay or prevent the supply of ICLUSIG to Apotex.

We are available at your convenience to answer any questions or provide any information you reasonably require.

Thank you,

Adam Rambert
Assistant General Counsel

Apotex
150 Signet Drive, Toronto, ON M9L 1T9
T: 416-401-7334 | M: 647-532-8174 | arambert@apotex.com | www.apotex.com

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From: Nikas, Alex <Nikas.Alexander@endo.com>
Sent: Friday, September 8, 2023 9:50 AM
To: Adam Rambert <arambert@apotex.com>
Cc: Katharine Weekes <kweekes@apotex.com>; Trempe, Isabelle <Trempe.Isabelle@endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>; "Matthew Castellarin" <matthew.castellarin@takeda.com>; heather.eck@takeda.com
Subject: iClusig (Ponatinib Hydrochloride) supply in Canada

Dear Mr. Rambert,

I am an attorney with Endo Pharmaceuticals, a US affiliate of Paladin Labs, distributor of iClusig (Ponatinib Hydrochloride) in Canada. We are in receipt of your correspondence of August 24, 2023. We have conferred with our US and Canadian colleagues at Takeda and determined that the most expeditious way for Apotex to procure supply of iClusig in Canada is to set up an account and place an order through Paladin Labs Customer Service Department. The contact information is below. Should you encounter any difficulties please contact us and we will work to resolve them.

Paladin Toll Free: 1-866-340-1112
Paladin Fax: 1-866-340-7221
Email: customerservicepaladin@paladinlabs.com

Regards,

Alex

Alexander A. Nikas
VP & AGC Global Commercial Ops and R&D

office 484-216-6736
mobile **445-787-2351**
Nikas.Alexander@endo.com

Endo
1400 Atwater Drive
Malvern, PA 19355

endo.com

This is **Exhibit "22"** referred to in the Affidavit sworn remotely by Nick Boorman, stated as being at the City of Toronto, in the Province of Ontario, before me at the City of Toronto, in the Province of Ontario, on September 29, 2023, in accordance with O. Reg. 431/20, *Administering Oath or Declaration Remotely*

A Commissioner, etc.

Exhibit "23"

From: De Serres, Jean <DeSerres.Jean@Endo.com>
Sent: Monday, September 18, 2023 9:38 AM
To: Nikas, Alex <Nikas.Alexander@endo.com>; Adam Rambert <arambert@apotex.com>; Trempe, Isabelle <Trempe.Isabelle@endo.com>; Paladin - Customer Service <customerservicepaladin@paladin-labs.com>
Cc: Kennedy, Kristin <Kennedy.Kristin@endo.com>; matthew.castellarin@takeda.com; heather.eck@takeda.com; Di Francesco, Livio <DiFrancesco.Livio@Endo.com>; Katharine Weekes <kweekes@apotex.com>
Subject: Re: [EXTERNAL] RE: Establish new account for Apotex, and order for ICLUSIG

Hello
There is no shortage but low inventory and this is a very small volume product: a few patients make a significant impact. When we have volume secured, we will let you know
Regards
Jean

De : Nikas, Alex <Nikas.Alexander@endo.com>
Envoyé : Monday, September 18, 2023 9:27:18 AM
À : Adam Rambert <arambert@apotex.com>; Trempe, Isabelle <Trempe.Isabelle@endo.com>; Paladin - Customer Service <customerservicepaladin@paladin-labs.com>
Cc : Kennedy, Kristin <Kennedy.Kristin@endo.com>; matthew.castellarin@takeda.com <matthew.castellarin@takeda.com>; heather.eck@takeda.com <heather.eck@takeda.com>; Di Francesco, Livio <DiFrancesco.Livio@Endo.com>; Katharine Weekes <kweekes@apotex.com>; De Serres, Jean <DeSerres.Jean@Endo.com>
Objet : RE: [EXTERNAL] RE: Establish new account for Apotex, and order for ICLUSIG

Dear Adam,

We will discuss your requests internally and revert.

Regards,

Alex

Alexander A. Nikas
VP & AGC Global Commercial Ops and R&D

office 484-216-6736
mobile **445-787-2351**
Nikas.Alexander@endo.com

Endo
1400 Atwater Drive
Malvern, PA 19355

endo.com

From: Adam Rambert <arambert@apotex.com>
Sent: Monday, September 18, 2023 9:24 AM
To: Trempe, Isabelle <Trempe.Isabelle@endo.com>; Paladin - Customer Service <customerservicepaladin@paladin-labs.com>
Cc: Nikas, Alex <Nikas.Alexander@endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>; matthew.castellarin@takeda.com; heather.eck@takeda.com; Di Francesco, Livio <DiFrancesco.Livio@Endo.com>; Katharine Weekes <kweekes@apotex.com>; De Serres, Jean <DeSerres.Jean@Endo.com>
Subject: RE: [EXTERNAL] RE: Establish new account for Apotex, and order for ICLUSIG

Dear Isabelle,

Thanks for getting back to us. We have checked www.drugshortagescanada.ca; no report has been filed for ICLUSIG. We are seeking only the delivery of 360 pills. You will appreciate the reasons why Apotex is highly skeptical that the requested supply is not available or cannot be made available. Regardless, will Paladin write to Takeda (whose representatives are copied on this email chain), requesting that Takeda ship by express courier 360 pills to Paladin for delivery in the next three business days, so that those pills can be delivered to Apotex? We see no impediment to Paladin making this request of Takeda, in writing, today. Please copy me on that correspondence.

Dear Alex,

Endo distributes ICLUSIG in Canada. What action will Endo take to immediately resolve this situation? Will Endo contact Takeda, to request that Takeda ship by express courier 360 pills to Paladin for delivery in the next three business days, so that those pills can be delivered to Apotex? We see no impediment to Endo making this request of Takeda, in writing, today. Please copy myself on that correspondence.

Dear Matthew,

ICLUSIG is marketed by Takeda in Canada. What action will Takeda take to immediately resolve this situation? Will Takeda ship by express courier 360 pills to Paladin for delivery in the next three business days, so that those pills can be delivered to Apotex (in response to a request from Endo / Paladin, or otherwise)?

Apotex stands ready to support the efforts of each of your companies to deliver the requested order. Apotex is willing to reimburse all reasonable courier charges. Apotex is prejudiced by every additional day of delay that occurs for the supply of the requested order.

Regards,

Adam Rambert
Assistant General Counsel

Apotex
150 Signet Drive, Toronto, ON M9L 1T9
T: 416-401-7334 | M: 647-532-8174 | arambert@apotex.com | www.apotex.com

---

From: Trempe, Isabelle <Trempe.Isabelle@endo.com>
Sent: Sunday, September 17, 2023 8:49 PM
To: Adam Rambert <arambert@apotex.com>; Paladin - Customer Service <customerservicepaladin@paladin-labs.com>
Cc: Nikas, Alex <Nikas.Alexander@endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>; matthew.castellarin@takeda.com; heather.eck@takeda.com; Di Francesco, Livio <DiFrancesco.Livio@Endo.com>; Katharine Weekes <kweekes@apotex.com>; De Serres, Jean <DeSerres.Jean@Endo.com>
Subject: RE: [EXTERNAL] RE: Establish new account for Apotex, and order for ICLUSIG

> **Caution:** This is an external email. Please take care when clicking links or opening attachments. When in doubt, contact the Global Service Desk.

Dear Adam, We have less than 2 months of stock and cannot jeopardize the patient continuity of stock with this rather large volume request. We will let you know when we receive and release next lot which is expected in the next month. We also asked (Jean De Serres email) confirmation of use: for human or not. We need this to be answered since the product is on CDP and we need to certify prescriber and pharmacist before shipping if for use by humans.

Kind regards, isabelle

Vice-présidente, Opérations commerciales / Accès aux marchés -
Vice President, Commercial Operations / Market Access
100 Boul. Alexis-Nihon, Bureau/Suite 600 Montréal, QC, H4M 2P2 Canada
trempe.isabelle@endo.com
www.paladinlabs.com

From: Adam Rambert <arambert@apotex.com>
Sent: Friday, September 15, 2023 12:25 PM
To: Paladin - Customer Service <customerservicepaladin@paladin-labs.com>
Cc: Nikas, Alex <Nikas.Alexander@endo.com>; Trempe, Isabelle <Trempe.Isabelle@endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>; matthew.castellarin@takeda.com; heather.eck@takeda.com; Di Francesco, Livio <DiFrancesco.Livio@Endo.com>; Lam, Jason <Lam.Jason@endo.com>; Katharine Weekes <kweekes@apotex.com>
Subject: [EXTERNAL] RE: Establish new account for Apotex, and order for ICLUSIG

Dear Paladin Labs – I'm following from my email of September 8, below. As noted, we require the supply of this drug very promptly. What can we do to expedite this transaction? Thanks in advance for your quick reply.

@Alex Nikas – Please let us know ASAP if there is another person or email address at Paladin Labs whom we should contact for this order, or if there is any other reason why the order we have requested has not been fulfilled promptly.

Regards,

Adam Rambert
Assistant General Counsel

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---

From: Adam Rambert
Sent: Friday, September 8, 2023 2:47 PM
To: customerservicepaladin@paladinlabs.com
Cc: nikas.alexander@endo.com; trempe.isabelle@endo.com; kennedy.kristin@endo.com; matthew.castellarin@takeda.com; heather.eck@takeda.com; difrancesco.livio@endo.com; lam.jason@endo.com; Katharine Weekes <kweekes@apotex.com>
Subject: Establish new account for Apotex, and order for ICLUSIG

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On August 24, we wrote to Paladin Labs (and Takeda and Endo) to request the supply of 6 packs of 60 15 mg tablets of ICLUSIG (ponatinib hydrochloride) – in other words, 360 15 mg tablets. See the attached correspondence.

Per the email below, Endo and Takeda have instructed Apotex to contact you to establish an account and place the requested order. Please set out the information you require to establish an account in the name of Apotex Inc. As noted in our August 24 letter, we require the supply of this product very promptly, and therefore your cooperation to establish our account and fulfill our order is much appreciated. We understand that ICLUSIG is subject to a Risk Management Plan; as your counsel will advise you, that plan should not delay or prevent the supply of ICLUSIG to Apotex.

We are available at your convenience to answer any questions or provide any information you reasonably require.

Thank you,

Adam Rambert
Assistant General Counsel

Apotex
150 Signet Drive, Toronto, ON M9L 1T9
T: 416-401-7334 | M: 647-532-8174 | arambert@apotex.com | www.apotex.com

---

From: Nikas, Alex <Nikas.Alexander@endo.com>
Sent: Friday, September 8, 2023 9:50 AM
To: Adam Rambert <arambert@apotex.com>
Cc: Katharine Weekes <kweekes@apotex.com>; Trempe, Isabelle <Trempe.Isabelle@endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>; "Matthew Castellarin" <matthew.castellarin@takeda.com>; heather.eck@takeda.com
Subject: iClusig (Ponatinib Hydrochloride) supply in Canada

Dear Mr. Rambert,

I am an attorney with Endo Pharmaceuticals, a US affiliate of Paladin Labs, distributor of iClusig (Ponatinib Hydrochloride) in Canada. We are in receipt of your correspondence of August 24, 2023. We have conferred with our US and Canadian colleagues at Takeda and determined that the most expeditious way for Apotex to procure supply of iClusig in Canada is to set up an account and place an order through Paladin Labs Customer Service Department. The contact information is below. Should you encounter any difficulties please contact us and we will work to resolve them.

Paladin Toll Free: 1-866-340-1112
Paladin Fax: 1-866-340-7221
Email: customerservicepaladin@paladinlabs.com

Regards,

Alex

Alexander A. Nikas
VP & AGC Global Commercial Ops and R&D

office 484-216-6736
mobile **445-787-2351**
Nikas.Alexander@endo.com

Endo
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Malvern, PA 19355

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This e-mail transmission, including any attachments, is intended only for the individual(s) or entity(ies) named in the e-mail address and may contain confidential or proprietary information that may be subject to protections afforded to certain types of confidential and/or proprietary information, including attorney-client privilege. If you have any reason to believe that you are not the intended recipient or an agent responsible for delivering it to the intended recipient, you are hereby notified that any review, use, disclosure, copying, distribution, or reliance upon the contents of this e-mail transmission, and any attachments thereto, is strictly prohibited. If you have received this e-mail transmission in error, please notify the sender immediately, so that Endo can arrange for proper delivery, and then please permanently delete the original and any copy of this e-mail transmission from your system and any printout thereof. Thank you.

This is **Exhibit "23"** referred to in the Affidavit sworn remotely by Nick Boorman, stated as being at the City of Toronto, in the Province of Ontario, before me at the City of Toronto, in the Province of Ontario, on September 29, 2023, in accordance with O. Reg. 431/20, *Administering Oath or Declaration Remotely*

A Commissioner, etc.

Exhibit “24”

From: Adam Rambert
Sent: Wednesday, September 20, 2023 9:59 AM
To: Paladin - Credit <Paladin-Credit@endo.com>
Cc: matthew.castellarin@takeda.com; heather.eck@takeda.com; PaladinCS <PaladinCS@endo.com>; Robertson, Myriah <Robertson.Kathryn2@endo.com>; De Serres, Jean <DeSerres.Jean@Endo.com>; Nikas, Alex <Nikas.Alexander@endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>
Subject: RE: [EXTERNAL] RE: Establish new account for Apotex, and order for ICLUSIG

Dear Annie,

Thanks for the email. Please find enclosed a completed credit application.

However, Apotex notes that it did not request and does not require a line of credit from Paladin, as Apotex is placing only a single order. If requested, Apotex will simply pay for the requested ICLUSIG pursuant to the terms indicated in Paladin's Terms and Conditions of Sale on its website (i.e., net 30 days). Apotex would also consider other reasonable payment terms, if Paladin so requests. Whether Paladin expeditiously approves Apotex's credit application or simply ships the requested ICLUSIG to Apotex on the standard Terms and Conditions of Sale is of no matter to Apotex; however, Paladin may not further delay its shipment to Apotex on account of an unrequested credit application.

Your email references a "QA Agreement." Please forward that agreement, and any other paperwork that Paladin requests that Apotex execute to complete Apotex's order, without any further delay. As noted in this email chain, Apotex is only willing to agree to reasonable commercial terms for a transaction of this type. Unreasonable commercial demands (i.e., establishment of a credit account that Apotex has not requested), unreasonable commercial terms, or further delay are not acceptable.

As noted in our letter of August 24, Apotex has requested that this straightforward transaction be completed within 20 business days, which is this Friday, September 22. Apotex remains available to discuss how this transaction can be expedited, to permit delivery by the end of this week.

Regards,

Adam Rambert

Assistant General Counsel

Apotex
150 Signet Drive, Toronto, ON M9L 1T9
T: 416-401-7334 | M: 647-532-8174 | arambert@apotex.com | www.apotex.com

---

From: Paladin - Credit <Paladin-Credit@endo.com>
Sent: Tuesday, September 19, 2023 9:01 AM
To: Adam Rambert <arambert@apotex.com>
Cc: matthew.castellarin@takeda.com; heather.eck@takeda.com; Katharine Weekes <kweekes@apotex.com>; PaladinCS <PaladinCS@endo.com>; Robertson, Myriah <Robertson.Kathryn2@endo.com>; De Serres, Jean <DeSerres.Jean@Endo.com>; Nikas, Alex <Nikas.Alexander@endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>
Subject: RE: [EXTERNAL] RE: Establish new account for Apotex, and order for ICLUSIG

> **Caution:** This is an external email. Please take care when clicking links or opening attachments. When in doubt, contact the Global Service Desk.

Hello Mr. Rambert,

Please find enclose credit application that you will need to complete.

If you could provide us with two trade references with their email address.

Also I am including the EFT letter from our bank if you would like to pay us EFT.

Once the application is complete I will have it review and a QA agreement will also have to be signed with your company.

Let me know if you have any questions.

Waiting for your complete application form.
Regards,
Annie

ANNIE ETHIER
Associée crédit, retours et créances/ Credit, Returns & Receivable Associate

Bureau | office 1-866-340-1112 / paladin-credit@Endo.com
Bureau | office ou 514-215-8454 / Ethier.Annie@Endo.com
Mobile 438-885-2664
Fax 1-877-997-4756

Laboratoires Paladin *une compagnie de endo* | **Paladin Labs Inc.** *an endo company*
100 Boulevard Alexis Nihon, Bureau 600
Montréal, QC H4M 2P2

From: PaladinCS <PaladinCS@endo.com>
Sent: Monday, September 18, 2023 8:29 AM
To: Adam Rambert <arambert@apotex.com>; Paladin - Customer Service <customerservicepaladin@paladin-labs.com>; Paladin - Credit <Paladin-Credit@endo.com>

Cc: Nikas, Alex <Nikas.Alexander@endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>; matthew.castellarin@takeda.com; heather.eck@takeda.com; Di Francesco, Livio <DiFrancesco.Livio@Endo.com>; Katharine Weekes <kweekes@apotex.com>; De Serres, Jean <DeSerres.Jean@Endo.com>; Trempe, Isabelle <Trempe.Isabelle@endo.com>
Subject: RE: [EXTERNAL] RE: Establish new account for Apotex, and order for ICLUSIG

Good morning,
Our finance team will be in contact with you for the new account creation.

Regards,

Ionela Proca

Chef des opérations
Operations Manager

bureau | **office** 514-215-8414
mobile 514-348-8922
fax 1.866.340.7221
proca.ionela@endo.com

Laboratoires Paladin *une compagnie de endo* | **Paladin Labs Inc.** *an endo company*
100 Boulevard Alexis Nihon, Bureau 600
Montréal, QC H4M2P2

endo.com
paladin-labs.com

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Cc: Nikas, Alex <Nikas.Alexander@endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>; matthew.castellarin@takeda.com; heather.eck@takeda.com; Di Francesco, Livio <DiFrancesco.Livio@Endo.com>; Katharine Weekes <kweekes@apotex.com>; De Serres, Jean <DeSerres.Jean@Endo.com>
Subject: RE: [EXTERNAL] RE: Establish new account for Apotex, and order for ICLUSIG

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Kind regards, isabelle

Vice-présidente, Opérations commerciales / Accès aux marchés -
Vice President, Commercial Operations / Market Access
100 Boul. Alexis-Nihon, Bureau/Suite 600 Montréal, QC, H4M 2P2 Canada
trempe.isabelle@endo.com
www.paladinlabs.com

From: Adam Rambert <arambert@apotex.com>
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To: Paladin - Customer Service <customerservicepaladin@paladin-labs.com>
Cc: Nikas, Alex <Nikas.Alexander@endo.com>; Trempe, Isabelle <Trempe.Isabelle@endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>; matthew.castellarin@takeda.com; heather.eck@takeda.com; Di Francesco, Livio <DiFrancesco.Livio@Endo.com>; Lam, Jason <Lam.Jason@endo.com>; Katharine Weekes <kweekes@apotex.com>
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@Alex Nikas – Please let us know ASAP if there is another person or email address at Paladin Labs whom we should contact for this order, or if there is any other reason why the order we have requested has not been fulfilled promptly.

Regards,

Adam Rambert
Assistant General Counsel

Apotex
150 Signet Drive, Toronto, ON M9L 1T9
T: 416-401-7334 | M: 647-532-8174 | arambert@apotex.com | www.apotex.com

---

From: Adam Rambert
Sent: Friday, September 8, 2023 2:47 PM
To: customerservicepaladin@paladinlabs.com
Cc: nikas.alexander@endo.com; trempe.isabelle@endo.com; kennedy.kristin@endo.com; matthew.castellarin@takeda.com; heather.eck@takeda.com; difrancesco.livio@endo.com; lam.jason@endo.com; Katharine Weekes <kweekes@apotex.com>
Subject: Establish new account for Apotex, and order for ICLUSIG

Dear Paladin Labs,

On August 24, we wrote to Paladin Labs (and Takeda and Endo) to request the supply of 6 packs of 60 15 mg tablets of ICLUSIG (ponatinib hydrochloride) – in other words, 360 15 mg tablets. See the attached correspondence.

Per the email below, Endo and Takeda have instructed Apotex to contact you to establish an account and place the requested order. Please set out the information you require to establish an account in the name of Apotex Inc. As noted in our August 24 letter, we require the supply of this product very promptly, and therefore your cooperation to establish

our account and fulfill our order is much appreciated. We understand that ICLUSIG is subject to a Risk Management Plan; as your counsel will advise you, that plan should not delay or prevent the supply of ICLUSIG to Apotex.

We are available at your convenience to answer any questions or provide any information you reasonably require.

Thank you,

Adam Rambert
Assistant General Counsel

Apotex
150 Signet Drive, Toronto, ON M9L 1T9
T: 416-401-7334 | M: 647-532-8174 | arambert@apotex.com | www.apotex.com

---

From: Nikas, Alex <Nikas.Alexander@endo.com>
Sent: Friday, September 8, 2023 9:50 AM
To: Adam Rambert <arambert@apotex.com>
Cc: Katharine Weekes <kweekes@apotex.com>; Trempe, Isabelle <Trempe.Isabelle@endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>; "Matthew Castellarin" <matthew.castellarin@takeda.com>; heather.eck@takeda.com
Subject: iClusig (Ponatinib Hydrochloride) supply in Canada

Dear Mr. Rambert,

I am an attorney with Endo Pharmaceuticals, a US affiliate of Paladin Labs, distributor of iClusig (Ponatinib Hydrochloride) in Canada. We are in receipt of your correspondence of August 24, 2023. We have conferred with our US and Canadian colleagues at Takeda and determined that the most expeditious way for Apotex to procure supply of iClusig in Canada is to set up an account and place an order through Paladin Labs Customer Service Department. The contact information is below. Should you encounter any difficulties please contact us and we will work to resolve them.

Paladin Toll Free: 1-866-340-1112
Paladin Fax: 1-866-340-7221
Email: customerservicepaladin@paladinlabs.com

Regards,

Alex

Alexander A. Nikas
VP & AGC Global Commercial Ops and R&D

office 484-216-6736
mobile **445-787-2351**
Nikas.Alexander@endo.com

Endo
1400 Atwater Drive
Malvern, PA 19355

endo.com

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This is **Exhibit "24"** referred to in the Affidavit sworn remotely by Nick Boorman, stated as being at the City of Toronto, in the Province of Ontario, before me at the City of Toronto, in the Province of Ontario, on September 29, 2023, in accordance with O. Reg. 431/20, *Administering Oath or Declaration Remotely*

A Commissioner, etc.

Exhibit "25"

From: Adam Rambert
Sent: Thursday, September 21, 2023 1:31 PM
To: 'Nikas, Alex' <Nikas.Alexander@endo.com>; Paladin - Credit <Paladin-Credit@endo.com>
Cc: matthew.castellarin@takeda.com; heather.eck@takeda.com; PaladinCS <PaladinCS@endo.com>; Robertson, Myriah <Robertson.Kathryn2@endo.com>; De Serres, Jean <DeSerres.Jean@Endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>; Trempe, Isabelle <Trempe.Isabelle@endo.com>; Di Francesco, Livio <DiFrancesco.Livio@Endo.com>
Subject: RE: [EXTERNAL] RE: Establish new account for Apotex, and order for ICLUSIG

Dear Alex,

Thank you for your email.

Apotex knows of no barrier to Paladin simply supplying Apotex with ICLUSIG from its existing stocks. Apotex's order is for a small volume of product only (360 pills). Moreover, Apotex repeated its order on August 24. If it is correct that Paladin did not have sufficient supply at that time to fulfill Apotex's order, Apotex expects that 20 business days was more than sufficient time for Paladin to place an order for additional supplies from Takeda and subject those supplies to Paladin's quality assurance procedures. Paladin's Customer Service department did not reply to Apotex's August 24 request until September 17. Apotex cannot be responsible for delays that are not commercially reasonable.

Thank you for your confirmation that no Quality Assurance agreement is required for the delivery of this product. Please confirm that no other agreements or other paperwork (other than a purchase order, payment instructions or similar basic documents) are required to complete this transaction.

Thank you for your confirmation that no aspect of the ICLUSIG Controlled Distribution Program will delay shipment of Apotex's order. As noted, Apotex is interested in better understanding the best practices that Paladin has established for ICLUSIG, and I invite Dr. De Serres to forward relevant materials to me at his earliest convenience. I will work with our team to ensure the information is put in the right hands at Apotex, and I may put responsible Apotex team members in direct contact with Dr. De Serres. Apotex cannot speak to whether it is appropriate or advisable for Apotex to become "certified" or "trained" under the ICLUSIG Controlled Distribution Program, as Apotex does not have information about the program at this time.

Please confirm that Apotex can expect delivery of the requested product by the close of business tomorrow (September 22).

Adam Rambert
Assistant General Counsel

Apotex
150 Signet Drive, Toronto, ON M9L 1T9
T: 416-401-7334 | M: 647-532-8174 | arambert@apotex.com | www.apotex.com

---

From: Nikas, Alex <Nikas.Alexander@endo.com>
Sent: Thursday, September 21, 2023 11:42 AM
To: Adam Rambert <arambert@apotex.com>; Paladin - Credit <Paladin-Credit@endo.com>
Cc: matthew.castellarin@takeda.com; heather.eck@takeda.com; PaladinCS <PaladinCS@endo.com>; Robertson, Myriah <Robertson.Kathryn2@endo.com>; De Serres, Jean <DeSerres.Jean@Endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>; Trempe, Isabelle <Trempe.Isabelle@endo.com>; Di Francesco, Livio <DiFrancesco.Livio@Endo.com>
Subject: RE: [EXTERNAL] RE: Establish new account for Apotex, and order for ICLUSIG

Dear Mr. Rambert,

The QA release process will occur over the next several days, but I cannot give you a precise date. As I am sure that Apotex can appreciate as a fellow pharmaceutical manufacturer, QA processes cannot be rushed. Once the product is released we will ship without undue delay.

I was able to confirm that no quality agreement with Apotex is required for this purchase, which was an open item from previous correspondence.

Thank you for confirming human use. Regarding the CDP certification, Paladin has an obligation under the CDP to ensure prescribers of ICLUSIG are adequately trained on its risks. Please see information available at Iclusig (iclusigcdp.ca). We recognize that there is no prescriber in this situation, which is why we requested the contact information of the personnel who will use the product so we can feel comfortable that we have met our obligation. If Apotex declines to be trained and certified, we will note that in our records, but the shipment of product will not be delayed by a lack of certification.

Regards,

Alex

Alexander A. Nikas
VP & AGC Global Commercial Ops and R&D

office 484-216-6736
mobile **445-787-2351**
Nikas.Alexander@endo.com

Endo
1400 Atwater Drive
Malvern, PA 19355

endo.com

From: Adam Rambert <arambert@apotex.com>
Sent: Wednesday, September 20, 2023 1:49 PM
To: Nikas, Alex <Nikas.Alexander@endo.com>; Paladin - Credit <Paladin-Credit@endo.com>
Cc: matthew.castellarin@takeda.com; heather.eck@takeda.com; PaladinCS <PaladinCS@endo.com>; Robertson, Myriah <Robertson.Kathryn2@endo.com>; De Serres, Jean <DeSerres.Jean@Endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>; Trempe, Isabelle <Trempe.Isabelle@endo.com>; Di Francesco, Livio <DiFrancesco.Livio@Endo.com>
Subject: RE: [EXTERNAL] RE: Establish new account for Apotex, and order for ICLUSIG

Dear Alex,

Thanks for your email.

Thank you for confirming that Paladin will have sufficient supply as of today to fulfill Apotex's order expeditiously. How long do you expect that Paladin's "quality assurance" testing is likely to take? Apotex repeats its request for delivery by Friday.

The completed spreadsheet that Customer Service forwarded to us was attached to my email at 9:59 AM. If there is any other information required from Apotex to complete this transaction (including any other documentation), please let us know without further delay.

Per my email to Dr. Jean De Serres of September 18 at 10:27 AM, I again confirm that the ICLUSIG that Apotex has ordered is for human use.

Apotex's personnel are all highly qualified and have significant experience conducting bioequivalence testing (including for products that are subject to Risk Management Plans). Apotex holds itself to the highest standards. Apotex welcomes and would duly consider any training or other protocols that Dr. Jean De Serres would like to suggest to Apotex. Similarly, Apotex is not aware of any "certification" that Paladin (or Takeda or Endo) privately maintains as part of its Risk Management Plan for ICLUSIG, but Apotex welcomes and would duly consider any aspect of the certification standard that Dr. Jean De Serres would like to suggest to Apotex. However, the supply of the requested ICLUSIG or Apotex's conducting of a bioequivalence study cannot be conditioned or delayed on (i) Apotex receiving, accepting or implementing such training or other suggestions, or (ii) Apotex applying for or attaining any type of certification from Paladin (or Takeda or Endo).

I would be pleased to receive information from Dr. Jean De Serres at first instance. Based on that information, I can determine whether and who within Apotex would be best placed to interface with Dr. De Serres regarding those topics.

Regards,

Adam Rambert
Assistant General Counsel

Apotex
150 Signet Drive, Toronto, ON M9L 1T9
T: 416-401-7334 | M: 647-532-8174 | arambert@apotex.com | www.apotex.com

---

From: Nikas, Alex <Nikas.Alexander@endo.com>
Sent: Wednesday, September 20, 2023 10:56 AM
To: Adam Rambert <arambert@apotex.com>; Paladin - Credit <Paladin-Credit@endo.com>
Cc: matthew.castellarin@takeda.com; heather.eck@takeda.com; PaladinCS <PaladinCS@endo.com>; Robertson, Myriah <Robertson.Kathryn2@endo.com>; De Serres, Jean <DeSerres.Jean@Endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>; Trempe, Isabelle <Trempe.Isabelle@endo.com>; Di Francesco, Livio <DiFrancesco.Livio@Endo.com>
Subject: RE: [EXTERNAL] RE: Establish new account for Apotex, and order for ICLUSIG

Dear Mr. Rambert,

We have discussed internally and I can clarify what Paladin's situation is now. We are expecting a supply of ICLUSIG to be received today, and as soon as that shipment passes QA release we will have enough stock to fill your order expeditiously.

In the meantime we need Apotex to finish completing the financial documents that Customer Service provided to complete set up of the account to effect the purchase. Our finance group will need to respond to your request to not complete a credit application, but I understand your point about a one-time purchase.

Additionally, we need to confirm whether Apotex is using the product for human or non-human use. If for human use, we need you to provide Dr. Jean De Serres with the contact info for the Apotex personnel who will be responsible for using the product in humans so we may provide the required training and certification under the CDP.

We look forward to resolving this matter in the near future. Thank you for your understanding.

Regards,

Alex

Alexander A. Nikas
VP & AGC Global Commercial Ops and R&D

office 484-216-6736
mobile **445-787-2351**
Nikas.Alexander@endo.com

Endo
1400 Atwater Drive
Malvern, PA 19355

endo.com

From: Adam Rambert <arambert@apotex.com>
Sent: Wednesday, September 20, 2023 9:59 AM
To: Paladin - Credit <Paladin-Credit@endo.com>
Cc: matthew.castellarin@takeda.com; heather.eck@takeda.com; PaladinCS <PaladinCS@endo.com>; Robertson, Myriah <Robertson.Kathryn2@endo.com>; De Serres, Jean <DeSerres.Jean@Endo.com>; Nikas, Alex <Nikas.Alexander@endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>
Subject: RE: [EXTERNAL] RE: Establish new account for Apotex, and order for ICLUSIG

Dear Annie,

Thanks for the email. Please find enclosed a completed credit application.

However, Apotex notes that it did not request and does not require a line of credit from Paladin, as Apotex is placing only a single order. If requested, Apotex will simply pay for the requested ICLUSIG pursuant to the terms indicated in Paladin's Terms and Conditions of Sale on its website (i.e., net 30 days). Apotex would also consider other reasonable payment terms, if Paladin so requests. Whether Paladin expeditiously approves Apotex's credit application or simply ships the requested ICLUSIG to Apotex on the standard Terms and Conditions of Sale is of no matter to Apotex; however, Paladin may not further delay its shipment to Apotex on account of an unrequested credit application.

Your email references a "QA Agreement." Please forward that agreement, and any other paperwork that Paladin requests that Apotex execute to complete Apotex's order, without any further delay. As noted in this email chain, Apotex is only willing to agree to reasonable commercial terms for a transaction of this type. Unreasonable commercial demands (i.e., establishment of a credit account that Apotex has not requested), unreasonable commercial terms, or further delay are not acceptable.

As noted in our letter of August 24, Apotex has requested that this straightforward transaction be completed within 20 business days, which is this Friday, September 22. Apotex remains available to discuss how this transaction can be expedited, to permit delivery by the end of this week.

Regards,

Adam Rambert
Assistant General Counsel

Apotex
150 Signet Drive, Toronto, ON M9L 1T9
T: 416-401-7334 | M: 647-532-8174 | arambert@apotex.com | www.apotex.com

---

From: Paladin - Credit <Paladin-Credit@endo.com>
Sent: Tuesday, September 19, 2023 9:01 AM
To: Adam Rambert <arambert@apotex.com>

Cc: matthew.castellarin@takeda.com; heather.eck@takeda.com; Katharine Weekes <kweekes@apotex.com>; PaladinCS <PaladinCS@endo.com>; Robertson, Myriah <Robertson.Kathryn2@endo.com>; De Serres, Jean <DeSerres.Jean@Endo.com>; Nikas, Alex <Nikas.Alexander@endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>
Subject: RE: [EXTERNAL] RE: Establish new account for Apotex, and order for ICLUSIG

> **Caution:** This is an external email. Please take care when clicking links or opening attachments. When in doubt, contact the Global Service Desk.

Hello Mr. Rambert,

Please find enclose credit application that you will need to complete.

If you could provide us with two trade references with their email address.

Also I am including the EFT letter from our bank if you would like to pay us EFT.

Once the application is complete I will have it review and a QA agreement will also have to be signed with your company.

Let me know if you have any questions.

Waiting for your complete application form.
Regards,
Annie

ANNIE ETHIER
Associée crédit, retours et créances/ Credit, Returns & Receivable Associate

Bureau | office 1-866-340-1112 / **paladin-credit@Endo.com**
Bureau | office ou 514-215-8454 / Ethier.Annie@Endo.com
Mobile 438-885-2664
Fax 1-877-997-4756

Laboratoires Paladin *une compagnie de endo* | **Paladin Labs Inc.** *an endo company*
100 Boulevard Alexis Nihon, Bureau 600
Montréal, QC H4M 2P2

From: PaladinCS <PaladinCS@endo.com>
Sent: Monday, September 18, 2023 8:29 AM
To: Adam Rambert <arambert@apotex.com>; Paladin - Customer Service <customerservicepaladin@paladin-labs.com>; Paladin - Credit <Paladin-Credit@endo.com>
Cc: Nikas, Alex <Nikas.Alexander@endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>; matthew.castellarin@takeda.com; heather.eck@takeda.com; Di Francesco, Livio <DiFrancesco.Livio@Endo.com>; Katharine Weekes <kweekes@apotex.com>; De Serres, Jean <DeSerres.Jean@Endo.com>; Trempe, Isabelle <Trempe.Isabelle@endo.com>
Subject: RE: [EXTERNAL] RE: Establish new account for Apotex, and order for ICLUSIG

Good morning,
Our finance team will be in contact with you for the new account creation.

Regards,

Ionela Proca

Chef des opérations
Operations Manager

bureau | **office** 514-215-8414
mobile 514-348-8922
fax 1.866.340.7221
proca.ionela@endo.com

Laboratoires Paladin *une compagnie de endo* | **Paladin Labs Inc.** *an endo company*
100 Boulevard Alexis Nihon, Bureau 600
Montréal, QC H4M2P2

endo.com
paladin-labs.com

From: Trempe, Isabelle <Trempe.Isabelle@endo.com>
Sent: Sunday, September 17, 2023 8:49 PM
To: Adam Rambert <arambert@apotex.com>; Paladin - Customer Service <customerservicepaladin@paladin-labs.com>
Cc: Nikas, Alex <Nikas.Alexander@endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>; matthew.castellarin@takeda.com; heather.eck@takeda.com; Di Francesco, Livio <DiFrancesco.Livio@Endo.com>; Katharine Weekes <kweekes@apotex.com>; De Serres, Jean <DeSerres.Jean@Endo.com>
Subject: RE: [EXTERNAL] RE: Establish new account for Apotex, and order for ICLUSIG

Dear Adam, We have less than 2 months of stock and cannot jeopardize the patient continuity of stock with this rather large volume request. We will let you know when we receive and release next lot which is expected in the next month. We also asked (Jean De Serres email) confirmation of use: for human or not. We need this to be answered since the product is on CDP and we need to certify prescriber and pharmacist before shipping if for use by humans.

Kind regards, isabelle

Vice-présidente, Opérations commerciales / Accès aux marchés -
Vice President, Commercial Operations / Market Access
100 Boul. Alexis-Nihon, Bureau/Suite 600 Montréal, QC, H4M 2P2 Canada
trempe.isabelle@endo.com
www.paladinlabs.com

From: Adam Rambert <arambert@apotex.com>
Sent: Friday, September 15, 2023 12:25 PM
To: Paladin - Customer Service <customerservicepaladin@paladin-labs.com>
Cc: Nikas, Alex <Nikas.Alexander@endo.com>; Trempe, Isabelle <Trempe.Isabelle@endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>; matthew.castellarin@takeda.com; heather.eck@takeda.com; Di Francesco, Livio

<DiFrancesco.Livio@Endo.com>; Lam, Jason <Lam.Jason@endo.com>; Katharine Weekes <kweekes@apotex.com>
Subject: [EXTERNAL] RE: Establish new account for Apotex, and order for ICLUSIG

Dear Paladin Labs – I'm following from my email of September 8, below. As noted, we require the supply of this drug very promptly. What can we do to expedite this transaction? Thanks in advance for your quick reply.

@Alex Nikas – Please let us know ASAP if there is another person or email address at Paladin Labs whom we should contact for this order, or if there is any other reason why the order we have requested has not been fulfilled promptly.

Regards,

Adam Rambert
Assistant General Counsel

Apotex
150 Signet Drive, Toronto, ON M9L 1T9
T: 416-401-7334 | M: 647-532-8174 | arambert@apotex.com | www.apotex.com

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From: Adam Rambert
Sent: Friday, September 8, 2023 2:47 PM
To: customerservicepaladin@paladinlabs.com
Cc: nikas.alexander@endo.com; trempe.isabelle@endo.com; kennedy.kristin@endo.com; matthew.castellarin@takeda.com; heather.eck@takeda.com; difrancesco.livio@endo.com; lam.jason@endo.com; Katharine Weekes <kweekes@apotex.com>
Subject: Establish new account for Apotex, and order for ICLUSIG

Dear Paladin Labs,

On August 24, we wrote to Paladin Labs (and Takeda and Endo) to request the supply of 6 packs of 60 15 mg tablets of ICLUSIG (ponatinib hydrochloride) – in other words, 360 15 mg tablets. See the attached correspondence.

Per the email below, Endo and Takeda have instructed Apotex to contact you to establish an account and place the requested order. Please set out the information you require to establish an account in the name of Apotex Inc. As noted in our August 24 letter, we require the supply of this product very promptly, and therefore your cooperation to establish our account and fulfill our order is much appreciated. We understand that ICLUSIG is subject to a Risk Management Plan; as your counsel will advise you, that plan should not delay or prevent the supply of ICLUSIG to Apotex.

We are available at your convenience to answer any questions or provide any information you reasonably require.

Thank you,

Adam Rambert

Assistant General Counsel

Apotex
150 Signet Drive, Toronto, ON M9L 1T9
T: 416-401-7334 | M: 647-532-8174 | arambert@apotex.com | www.apotex.com

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From: Nikas, Alex <Nikas.Alexander@endo.com>
Sent: Friday, September 8, 2023 9:50 AM
To: Adam Rambert <arambert@apotex.com>
Cc: Katharine Weekes <kweekes@apotex.com>; Trempe, Isabelle <Trempe.Isabelle@endo.com>; Kennedy, Kristin <Kennedy.Kristin@endo.com>; "Matthew Castellarin" <matthew.castellarin@takeda.com>; heather.eck@takeda.com
Subject: iClusig (Ponatinib Hydrochloride) supply in Canada

Dear Mr. Rambert,

I am an attorney with Endo Pharmaceuticals, a US affiliate of Paladin Labs, distributor of iClusig (Ponatinib Hydrochloride) in Canada. We are in receipt of your correspondence of August 24, 2023. We have conferred with our US and Canadian colleagues at Takeda and determined that the most expeditious way for Apotex to procure supply of iClusig in Canada is to set up an account and place an order through Paladin Labs Customer Service Department. The contact information is below. Should you encounter any difficulties please contact us and we will work to resolve them.

Paladin Toll Free: 1-866-340-1112
Paladin Fax: 1-866-340-7221
Email: customerservicepaladin@paladinlabs.com

Regards,

Alex

Alexander A. Nikas
VP & AGC Global Commercial Ops and R&D

office 484-216-6736
mobile **445-787-2351**
Nikas.Alexander@endo.com

Endo
1400 Atwater Drive
Malvern, PA 19355

endo.com

please notify the sender immediately, so that Endo can arrange for proper delivery, and then please permanently delete the original and any copy of this e-mail transmission from your system and any printout thereof. Thank you.

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This e-mail transmission, including any attachments, is intended only for the individual(s) or entity(ies) named in the e-mail address and may contain confidential or proprietary information that may be subject to protections afforded to certain types of confidential and/or proprietary information, including attorney-client privilege. If you have any reason to believe that you are not the intended recipient or an agent responsible for delivering it to the intended recipient, you are hereby notified that any review, use, disclosure, copying, distribution, or reliance upon the contents of this e-mail transmission, and any attachments thereto, is strictly prohibited. If you have received this e-mail transmission in error, please notify the sender immediately, so that Endo can arrange for proper delivery, and then please permanently delete the original and any copy of this e-mail transmission from your system and any printout thereof. Thank you.

This is **Exhibit "25"** referred to in the Affidavit sworn remotely by Nick Boorman, stated as being at the City of Toronto, in the Province of Ontario, before me at the City of Toronto, in the Province of Ontario, on September 29, 2023, in accordance with O. Reg. 431/20, *Administering Oath or Declaration Remotely*

A Commissioner, etc.

The document that is being electronically submitted to the Tribunal is an electronic version of a paper document that has been signed by the affiant. The signed document in paper copy is available and will be produced if requested by the Tribunal.

David Rosner

Per:

GOODMANS LLP