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 administering in 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 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 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 advance research and development efforts.

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. In 2021, the FDA issued a complete response letter (CRL) in response to our New Drug Application for TAK-721 (budesonide oral suspension) for the treatment of eosinophilic esophagitis in which the FDA declined to approve the application and recommended an additional clinical study. Following receipt of the CRL, we decided not to pursue further development for TAK-721.

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 2022, the FDA issued a CRL in response to our Prior Approval Supplement (PAS) with respect to NATPARA (parathyroid hormone) to address the potential for rubber particulate formation and indicated that it could not approve the PAS in its current form. Takeda is continuing to evaluate the CRL to determine next steps. 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. 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 U.S. Food and Drug Administration (the “FDA”), the European Medicines Agency (the “EMA”), the Pharmaceuticals and Medical Devices Agency (the “PMDA”) in Japan and National Medical Products Administration (the “NMPA”) for China 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 a number of 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”). 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, and the submission of false claims for reimbursement by the federal government. 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., there has been increasing pricing pressure from managed care groups, as well as institutional and governmental purchasers. As managed care groups have grown in size due to market consolidation, pharmaceutical companies have faced increased pressure in pricing and usage negotiations, and there is fierce competition among pharmaceutical companies 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. There has been increasing attention paid to the level of pricing of pharmaceutical products by policymakers and stakeholders, which could lead to political pressure or legislative, regulatory or other efforts to introduce lower prices, and change how the pharmaceutical supply chain could operate. In addition, there are efforts by the federal government to 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. The future of U.S. healthcare legislation and regulation is uncertain, but 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"), a price list published by the Ministry of Health, Labour and Welfare of Japan (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 at 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. Any new legislation in this area would take at least two to three years to be adopted but 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 (the "MCOs"), 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 bortezomib, the active ingredient in *VELCADE*, one of our largest selling products in the U.S., competing bortezomib-containing products with different formulations have been introduced. Entry of generic bortezomib products, which is expected in 2022 due to the expiration of patent protection covering the formulation of *VELCADE* and pediatric regulatory exclusivity, is likely to result in further reduction in revenue. Patent protections covering *VYVANSE* are scheduled to expire in the U.S. in 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 the generic or biosimilar manufacturer is able to design around our patents, or if the 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, which, if successfully introduced, 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 milestones 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 milestone 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.

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, 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 dual-source certain key products and/or active ingredients, we currently rely on a single source for production of certain 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 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 Practice (the “GMP”) 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 adulterated or otherwise in violation of applicable laws; problems with manufacturing, quality assurance/quality control 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. Takeda is continuing to evaluate the CRL to determine next steps.

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 stem cell therapies present heightened or additional risks. The manufacture of biologics, including stem cell 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) 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, including a significant amount incurred in connection with the Shire Acquisition, 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 4,345.4 billion JPY as of March 31, 2022, 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) 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 may fail to realize the anticipated benefits of the Shire Acquisition and expect to continue to record significant expenses related to it.

On January 8, 2019, we acquired the entire issued and to-be-issued share capital of Shire plc. The ultimate success of the Shire Acquisition depends on our ability to realize the anticipated growth opportunities and synergies leading to cost savings we expect from combining the companies' businesses. The expected synergies of the Shire Acquisition and the projected cash costs necessary to achieve the synergies may be affected by changes in the overall economic, political and regulatory environment, including applicable tax regimes and fluctuations in foreign exchange rates, and the realization of the other risks relating to our business described herein.

Furthermore, in connection with the Shire Acquisition, we recorded significant intangible assets and, as a result, significant amortization expense in the fiscal years ended March 31, 2020, 2021 and 2022, and we expect to continue to record significant amounts of amortization expense in future fiscal years. We also recognized significant non-cash expenses relating to the unwinding of fair value adjustments to inventory as a component of cost of sales in the fiscal years ended March 31, 2020, 2021 and 2022; we expect to record a certain level of these expenses in the fiscal year ending March 31, 2023. In addition, we recorded significant amounts of goodwill, and, if we are unable to achieve the anticipated benefits of the acquisition, we could be required to recognize significant impairment losses related to such goodwill and to intangible assets recorded in connection with the acquisition, potentially up to their full value. See *"—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."* for further discussion on risks associated with impairments.

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.

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 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; 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, 2022, regions outside of Japan accounted for 81.5% of our consolidated revenue, with the U.S. in particular contributing 48.0% 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 emerging markets, which we define to include Russia/Commonwealth of Independent States ("CIS"), Latin America, Asia (excluding Japan) and Other (including the Middle East, Oceania and Africa). Our revenue from emerging markets was 456.4 billion JPY (or 12.8% of our total revenue) for the fiscal year ended March 31, 2022, 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, 2022, revenue attributable to Russia/CIS represented 1.7% 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, 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 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 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 be net-zero in greenhouse gas (GHG) emissions by 2040. However, we may be unable to meet this commitment given the significant technological and organization changes required. 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 carbon neutral 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 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 patients 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 them 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 spread of COVID-19 and implementation of remote working arrangements. 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 liabilities 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. While Takeda intends to appeal the TAC ruling and continues to assert that the AbbVie break fee is not subject to Irish tax, Takeda has recorded a tax provision for 491 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, 2022. See Note 32 to our audited consolidated financial statements included in this annual report.

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 changes 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 and it is anticipated the framework will be adopted into law and become effective for tax years starting in 2023. We are awaiting the final legislation and detailed guidance to assess the full implications in the jurisdictions in which we operate.

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 (the "PIPL"), 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

The COVID-19 pandemic may continue to negatively affect our business, operating results and financial condition.

The COVID-19 pandemic continues to affect our business activities, operations, financial condition and results of operations to varying degrees. We have taken a number of actions in response to the spread of COVID-19, including implementing remote work arrangements where possible, canceling non-essential business travel and decreasing in-person meetings between our sales representatives and prescribers.

In the early stages of the global pandemic, we placed a general pause on the initiation of new studies, as well as new patient enrollment for ongoing studies with a small number of exceptions. While most of those temporary pauses on clinical trials were lifted and resumed, we do anticipate a certain level of delays on some clinical studies due to the disruption. We have also seen limited impact on demand for our products to date as many of our medicines are for severe chronic or life-threatening diseases, without the requirement of a hospital elective procedure. However, an adverse effect due to the spread of COVID-19 was observed in certain therapeutic areas, especially in Neuroscience in the first several months of the outbreak, for reasons such as less frequent visits by patients to medical care providers, on the other hand, an expansion of certain products with a more convenient administration profile was observed in the early phase of the outbreak, although these trends recently normalized to pre-COVID-19 levels. In the second half of the year ended March 31, 2022, we experienced some disruption to certain products due to the spread of the Omicron variant, including shipping delays and fewer diagnostic procedures, but these issues have not had a material financial impact.

Further outbreaks and preventative or protective actions that governments, corporations or individuals may take in the future to contain the spread of COVID-19 may result in a period of further reduced operations, decreased product demand including due to reduced numbers of in-person meetings with prescribers, patient visits with physicians, vaccinations and elective surgeries, further delays in the start of clinical trials or other research and development efforts, business disruption for us and our suppliers, subcontractors, customers and other third parties with which we do business and potential delays or disruptions related to regulatory approvals. For example, due in part to the effects of COVID-19-related lockdowns in China on our ability to conduct clinical trials, as well as other factors such as the invasion of Ukraine, we have announced delays in our target approval filing dates for soticlestat and EXKIVITY for treatment of newly diagnosed non-small cell lung cancer. Further outbreaks and related actions may also prevent our suppliers, vendors or subcontractors from meeting their obligations to us, including the supply of plasma, which has no substitute, which could also impair our ability to meet our supply obligations or execute our business plans in a timely manner or at all, or require us to incur significant additional costs. Any costs associated with the COVID-19 outbreak may not be fully recoverable or adequately covered by insurance. Further outbreaks and related actions may also result in reduced customer demand or limit the ability of customers, including governments or government agencies, to perform their obligations to us, including making timely payments. Any of these factors, depending on the severity and duration of the outbreak and its effects, could have a material adverse effect on our business, results of operations and financial condition.

Although the impacts of COVID-19 to our financial condition and results of operations were relatively limited and we currently do not anticipate material liquidity and funding issues, we are unable to accurately predict future impacts to our business, operations, financial condition, results of operations, cash flow and our share price, given the dynamically and rapidly changing uncertain environment under COVID-19. If countermeasures by governments, corporations and individuals against COVID-19, including vaccinations, are unsuccessful and the COVID-19 pandemic spreads or there is a resurgence of the existing virus or a mutation thereof and the disruption to various aspects of business operations is prolonged, our financial condition, results of operations and cash flow may be adversely affected.

Further, to the extent COVID-19 adversely affects our operations and global economic conditions more generally, many of the other risks described in this "Risk Factors" section may materialize or be amplified, which could adversely affect our business, operating results and financial condition.

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, 2022, 81.5% 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 carbon neutrality 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, tsunamis and/or volcanic eruptions. Other events outside our control, such as war, civil or political unrest, 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 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, 2022, there were two wholesale distributors, AmerisourceBergen Corporation and McKesson Corporation, 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, 2022, we had goodwill of 4,407.7 billion JPY and intangible assets of 3,818.5 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, 2022, the carrying amount of investments accounted for using the equity method was 96.6 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.