UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2021

or

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

For the transition period from to

Commission File Number: 001-33500

JAZZ PHARMACEUTICALS PUBLIC LIMITED COMPANY
(Exact name of registrant as specified in its charter)

Ireland	**98-1032470**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**

Fifth Floor, Waterloo Exchange
Waterloo Road, Dublin 4, Ireland D04 E5W7
011-353-1-634-7800
(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

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

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Ordinary shares, nominal value $0.0001 per share	**JAZZ**	**The Nasdaq Stock Market LLC**

Securities registered pursuant to Section 12(g) of the Act:
None

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

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

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

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

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

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

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

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant, as of June 30, 2021, the last business day of the registrant's most recently completed second fiscal quarter, was approximately $10,591,497,500 based upon the last sale price reported for the registrant's ordinary shares on such date on The Nasdaq Global Select Market. The calculation of the aggregate market value of voting and non-voting common equity excludes 1,490,584 ordinary shares of the registrant held by executive officers, directors and shareholders that the registrant concluded were affiliates of the registrant on that date. Exclusion of such shares should not be construed to indicate that any such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the registrant or that such person is controlled by or under common control with the registrant.

As of February 22, 2022, a total of 61,738,841 ordinary shares, nominal value $0.0001 per share, of the registrant were outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Certain information required by Part III, Items 10-14 of this Form 10-K is incorporated by reference to the registrant's definitive Proxy Statement for the 2022 Annual General Meeting of Shareholders to be filed with the Securities and Exchange Commission pursuant to Regulation 14A. If such Proxy Statement is not filed within 120 days after the end of the fiscal year covered by this Form 10-K, such information will be included in an amendment to this Form 10-K to be filed within such 120-day period.

JAZZ PHARMACEUTICALS PLC
2021 ANNUAL REPORT ON FORM 10-K

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We own or have rights to various copyrights, trademarks, and trade names used in our business in the U.S. and/or other countries, including the following: Jazz Pharmaceuticals®, Xyrem® (sodium oxybate) oral solution, Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, Epidiolex® (cannabidiol) oral solution, Epidyolex® (the trade name in Europe and other countries outside the U.S. for Epidiolex), Sunosi® (solriamfetol), Defitelio® (defibrotide sodium), Defitelio® (defibrotide), CombiPlex®, Vyxeos® (daunorubicin and cytarabine) liposome for injection, Vyxeos® liposomal 44 mg/100 mg powder for concentrate for solution for infusion, Zepzelca® (lurbinectedin), Rylaze™ (recombinant Erwinia asparaginase) and Sativex® (nabiximols) oral solution. This report also includes trademarks, service marks and trade names of other companies. Trademarks, service marks and trade names appearing in this Annual Report on Form 10-K are the property of their respective owners.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, which are subject to the "safe harbor" created by those sections. Forward-looking statements are based on our management's beliefs and assumptions and on information currently available to our management. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "could," "would," "expect," "plan," "anticipate," "believe," "estimate," "project," "predict," "propose," "intend," "continue," "potential," "possible," "strive," "seek," "designed," "goal", "foreseeable," "likely," "unforeseen" and similar expressions intended to identify forward-looking statements. These statements involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance, time frames or achievements to be materially different from any future results, performance, time frames or achievements expressed or implied by the forward-looking statements. We discuss many of these risks, uncertainties and other factors in greater detail under Risk Factors in Part I, Item 1A of this Annual Report on Form 10-K. Given these risks, uncertainties and other factors, you should not place undue reliance on these forward-looking statements. In addition, our goals and objectives are aspirational and are not guarantees or promises that such goals and objectives will be met. Also, these forward-looking statements represent our estimates and assumptions only as of the date of this filing. You should read this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. We hereby qualify our forward-looking statements by our cautionary statements. Except as required by law, we assume no obligation to update our forward-looking statements publicly, or to update the reasons that actual results could differ materially from those anticipated in these forward-looking statements, even if new information becomes available in the future.

SUMMARY RISK FACTORS

Below is a summary of material factors that make an investment in our ordinary shares speculative or risky. Importantly, this summary does not address all of the risks and uncertainties that we face. Additional discussion of the risks and uncertainties summarized in this risk factor summary, as well as other risks and uncertainties that we face, can be found under "Risk Factors" in Part I, Item 1A of this Annual Report on Form 10-K. The below risk factor summary is qualified in its entirety by that more complete discussion of such risks and uncertainties. You should consider carefully the risks and uncertainties described under "Risk Factors" in Part I, Item 1A of this Annual Report on Form 10-K as part of your evaluation of an investment in our ordinary shares.

- Our inability to maintain or increase sales from our oxybate franchise would have a material adverse effect on our business, financial condition, results of operations and growth prospects.
- The introduction of new products in the U.S. market that compete with, or otherwise disrupt the market for, our oxybate products and product candidates would adversely affect sales of our oxybate products and product candidates.
- The distribution and sale of our oxybate products are subject to significant regulatory restrictions, including the requirements of a risk evaluation and mitigation strategy, or REMS, and safety reporting requirements, and these regulatory and safety requirements subject us to risks and uncertainties, any of which could negatively impact sales of Xywav® and Xyrem®.
- Our inability to maintain or increase sales of Epidiolex® /Epidyolex® would have a material adverse effect on our business, financial condition, results of operations and growth prospects.
- While we expect our oxybate products and Epidiolex/Epidyolex to remain the largest parts of our business, our success also depends on our ability to effectively commercialize other products in our neuroscience and oncology therapeutic areas.
- We face substantial competition from other companies, including companies with larger sales organizations and more experience working with large and diverse product portfolios, and face competition from generic drugs and potentially from non-FDA approved cannabidiol preparations.
- Adequate coverage and reimbursement from third party payors may not be available for our products and we may be unable to successfully contract for coverage from pharmacy benefit managers and other organizations; conversely, to secure coverage from these organizations, we may be required to pay rebates or other discounts or other restrictions to reimbursement, either of which could diminish our sales or adversely affect our ability to sell our products profitably.
- The pricing of pharmaceutical products has come under increasing scrutiny as part of a global trend toward healthcare cost containment and resulting changes in healthcare law and policy may impact our business in ways that we cannot currently predict, which could have a material adverse effect on our business and financial condition.

- In addition to access, coverage and reimbursement, the commercial success of our products depends upon their market acceptance by physicians, patients, third party payors and the medical community.
- Delays or problems in the supply of our products for sale or for use in clinical trials, loss of our single source suppliers or failure to comply with manufacturing regulations could materially and adversely affect our business, financial condition, results of operations and growth prospects.
- Our future success depends on our ability to successfully develop and obtain and maintain regulatory approvals for our late-stage product candidates and, if approved, to successfully launch and commercialize those product candidates.
- We may not be able to successfully identify and acquire or in-license additional products or product candidates to grow our business, and, even if we are able to do so, we may otherwise fail to realize the anticipated benefits of these transactions.
- Conducting clinical trials is costly and time-consuming, and the outcomes are uncertain. A failure to prove that our product candidates are safe and effective in clinical trials, or to generate data in clinical trials to support expansion of the therapeutic uses for our existing products, could materially and adversely affect our business, financial condition, results of operations and growth prospects.
- We may not realize the anticipated benefits and synergies from the acquisition of GW Pharmaceuticals plc.
- It is difficult and costly to protect our proprietary rights, and we may not be able to ensure their protection.
- We have incurred and may in the future incur substantial costs as a result of litigation or other proceedings relating to patents, other intellectual property rights and related matters, and we may be unable to protect our rights to, or commercialize, our products.
- Our business is currently adversely affected and could be materially and adversely affected in the future by the evolving effects of the COVID-19 pandemic and related global economic slowdown, including with respect to our commercialization efforts, clinical trial activity, research and development activities, supply chain and corporate development activities and other business operations.
- Significant disruptions of information technology systems or data security breaches could adversely affect our business.
- We are subject to significant ongoing regulatory obligations and oversight, which may result in significant additional expense and limit our ability to commercialize our products.
- If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs, we could be subject to additional reimbursement requirements, penalties, sanctions and fines, which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.
- We have incurred substantial debt, which could impair our flexibility and access to capital and adversely affect our financial position, and our business would be adversely affected if we are unable to service our debt obligations.
- To continue to grow our business, we will need to commit substantial resources, which could result in future losses or otherwise limit our opportunities or affect our ability to operate and grow our business.

NOTE REGARDING COMPANY REFERENCE

In this report, unless otherwise indicated or the context otherwise requires, all references to "Jazz Pharmaceuticals," "Jazz," "the registrant," "we," "us," and "our" refer to Jazz Pharmaceuticals plc and its consolidated subsidiaries.

PART I

Item 1. Business

Overview

Jazz Pharmaceuticals plc is a global biopharmaceutical company whose purpose is to innovate to transform the lives of patients and their families. We are dedicated to developing life-changing medicines for people with serious diseases - often with limited or no therapeutic options. We have a diverse portfolio of marketed medicines and novel product candidates, from early- to late-stage development, in neuroscience and oncology. Within these therapeutic areas, we strive to identify new options for patients by actively exploring small molecules and biologics, and through innovative delivery technologies and cannabinoid science.

Our strategy for growth is rooted in executing commercial launches and ongoing commercialization initiatives; advancing robust research and development, or R&D, programs and delivering impactful clinical results; effectively deploying capital to strengthen the prospects of achieving our short- and long-term goals through strategic corporate development; and delivering strong financial performance. We focus on patient populations with high unmet needs. We identify and develop differentiated therapies for these patients that we expect will be long-lived assets and that we can support with an efficient commercialization model. In addition, we leverage our efficient, scalable operating model and integrated capabilities across our global infrastructure to effectively reach patients around the world.

At the 40th Annual J.P. Morgan Healthcare Conference in January 2022, we announced our Vision 2025, which aims to deliver sustainable growth and enhanced value, driving our continued transformation to an innovative, high-growth global pharmaceutical leader. The three core components of our Vision 2025 focus on commercial execution, pipeline productivity and operational excellence.

Our lead marketed products are:

Neuroscience

- **Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution**, a product approved by the U.S. Food and Drug Administration, or FDA, in July 2020 and launched in the U.S. in November 2020 for the treatment of cataplexy or excessive daytime sleepiness, or EDS, in patients with narcolepsy aged seven years of age and older, and also approved by FDA in August 2021 for the treatment of idiopathic hypersomnia, or IH, in adults and launched in the U.S. in November 2021. Xywav contains 92% less sodium than Xyrem®;
- **Xyrem (sodium oxybate) oral solution**, a product approved by FDA and distributed in the U.S. for the treatment of both cataplexy and EDS in patients seven years of age and older with narcolepsy; Jazz also markets Xyrem in Canada for the treatment of cataplexy in patients with narcolepsy. Xyrem is also approved and distributed in Europe, Great Britain and other markets through a licensing agreement;
- **Epidiolex® (cannabidiol) oral solution**, a product approved by FDA and launched in the U.S. in 2018 by GW Pharmaceuticals plc, or GW, and currently indicated for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex, or TSC, in patients one year of age or older; in Europe (where it is marketed as Epidyolex®) and other markets, it is approved for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome, in conjunction with clobazam (EU and Great Britain only), in patients 2 years of age and older and for adjunctive treatment of seizures associated with TSC in patients 2 years of age and older;
- **Sunosi® (solriamfetol)**, a product approved by FDA and marketed in the U.S., Canada, Europe and Great Britain to improve wakefulness in adult patients with EDS associated with narcolepsy or obstructive sleep apnea, or OSA; and
- **Sativex® (nabiximols) oral solution**, a product approved and marketed in the U.K., Canada and other markets as treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis, or MS, who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy.

Oncology

- **Zepzelca® (lurbinectedin)**, a product approved by FDA in June 2020 and launched in the U.S. in July 2020 for the treatment of adult patients with metastatic small cell lung cancer, or SCLC, with disease progression on or after platinum-based chemotherapy; in Canada, Zepzelca was approved in September 2021 for the treatment of adults with Stage III or metastatic SCLC, who have progressed on or after platinum-containing therapy;

- **Rylaze™** (recombinant Erwinia asparaginase), a product approved by FDA in June 2021 and launched in the U.S. in July 2021 for use as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia, or ALL, or lymphoblastic lymphoma, or LBL, in adults and pediatric patients who have developed hypersensitivity to *E. coli*-derived asparaginase;
- **Vyxeos® (daunorubicin and cytarabine) liposome for injection**, a product approved in the U.S., Canada, Europe and Great Britain (marketed as Vyxeos® liposomal in Europe and Great Britain) for the treatment of adults with newly-diagnosed therapy-related acute myeloid leukemia, or t-AML, or AML with myelodysplasia-related changes (AML-MRC). An expanded indication was granted in the U.S. for the treatment of newly diagnosed t-AML or AML-MRC in pediatric patients aged 1 year and older; and
- **Defitelio® (defibrotide sodium)**, is a product approved in the U.S. and Brazil for the treatment of hepatic veno-occlusive disease, or VOD, with renal or pulmonary dysfunction following hematopoietic stem cell transplantation, or HSCT, and in Japan for the treatment of hepatic sinusoidal obstruction syndrome (hepatic-veno occlusive disease). It is currently approved in the EU, Great Britain, Canada, Israel, South Korea, Australia and Switzerland for the treatment of severe hepatic VOD, also known as sinusoidal obstructive syndrome, or SOS, in HSCT therapy. It is indicated in adults and pediatric patients over 1 month of age.

In 2021, consistent with our strategy, we continued to focus on research and development activities within our neuroscience and oncology therapeutic areas. For a summary of our ongoing research and development activities, see “Business—Research and Development” in this Part I, Item 1.

Acquisition of GW Pharmaceuticals

In May 2021, we acquired GW Pharmaceuticals plc, or GW. The total consideration paid by us for the entire issued share capital of GW was $7.2 billion. The acquisition, which we refer to as the GW Acquisition, closed on May 5, 2021. We acquired GW with the objective of broadening our neuroscience portfolio, further diversifying our revenue and driving sustainable, long-term value creation opportunities. GW was a global leader in discovering, developing, manufacturing and commercializing novel, regulatory approved therapeutics from its proprietary cannabinoid research platform to address a broad range of diseases. For further information regarding the GW Acquisition, please see Note 3 Business Combinations, Asset Acquisitions and Collaborations of the Notes to Consolidated Financial Statements, included in Part IV of this Annual Report on Form 10-K.

Our Commercialized Products

Neuroscience

Xywav. Xywav is a product approved by FDA for the treatment of cataplexy or EDS in both adult and pediatric patients aged seven years of age and older with narcolepsy and for the treatment of adults with IH. Xywav is an oxybate product that contains 92% less sodium than Xyrem.

In July 2020, FDA approved Xywav for the treatment of both cataplexy and EDS in patients with narcolepsy. We commenced the U.S. launch in November 2020. We met our goal to obtain broad payor coverage of Xywav within six months of launch. To date, we have entered into agreements with various entities and have achieved benefit coverage for Xywav for approximately 90% of commercial lives.

Narcolepsy is a chronic, debilitating neurological disorder characterized by EDS and the inability to regulate sleep-wake cycles normally. It affects an estimated one in 2,000 people in the U.S., with symptoms typically appearing in childhood. There are five primary symptoms of narcolepsy, including EDS, cataplexy, disrupted nighttime sleep, sleep-related hallucinations, and sleep paralysis. While patients with narcolepsy may not experience all five symptoms, EDS, an essential symptom of narcolepsy, is present in all narcolepsy patients and is characterized by chronic, pervasive sleepiness as well as sudden irresistible and overwhelming urges to sleep (inadvertent naps and sleep attacks). Narcolepsy may affect many areas of life, including limiting a patient’s education and employment opportunities, and may lead to difficulties at work, school, or in daily life activities like driving, operating machinery or caring for children. Patients with narcolepsy may also suffer from significant medical comorbidities, including cardiac disorders, depression, suicide risk, anxiety, diseases of the digestive system and respiratory diseases.

Cataplexy, the sudden loss of muscle tone with retained consciousness, can be one of the most debilitating symptoms of narcolepsy. Cataplexy is present in approximately 70% of patients with narcolepsy. Cataplexy can range from slight weakness or a drooping of facial muscles to the complete loss of muscle tone resulting in postural collapse. It may also impair a patient’s vision or speech. Cataplexy is often triggered by strong emotions such as laughter, anger or surprise. Cataplexy can severely impair a patient’s quality of life and ability to function.

Narcolepsy patients, by virtue of their diagnosis, are at increased risk of cardiovascular events and disease, and the impact of sodium on cardiovascular health is well established. There is also extensive scientific evidence that reducing sodium

consumption, which is a modifiable risk factor, is associated with clinically meaningful reductions in blood pressure and cardiovascular disease risk. Therefore, we believe that reducing sodium intake compared to the standard of care by 92% each and every day is a significant advancement for these patients. The 92% reduction of sodium translates into a reduction of approximately 1,000 to 1,500 milligrams per day for a patient prescribed Xyrem, depending on the dose. When patients transition from Xyrem to Xywav, Xywav treatment is initiated at the same dose and regimen (gram for gram) and titrated as needed based on efficacy and tolerability. The label for Xywav, unlike Xyrem, does not include a warning to prescribers to monitor patients sensitive to sodium intake, including patients with heart failure, hypertension or renal impairment.

Our internal market research finds that health care providers and patients who understand the increased risk of cardiovascular disease faced by narcolepsy patients and who have been educated on the meaningful reduction in sodium from Xyrem to Xywav cite that meaningful reduction as a key reason for prescribing or starting on Xywav. In June 2021, FDA recognized seven years of Orphan Drug Exclusivity, or ODE, for Xywav in narcolepsy through July 21, 2027, stating that Xywav is clinically superior to Xyrem by means of greater safety due to reduced chronic sodium burden.

In approving Xywav, FDA approved a REMS to cover both Xywav and Xyrem. The Xywav and Xyrem REMS has the same requirements for both products and both products are also distributed by the central pharmacy through exclusive agreements described more fully below.

On August 12, 2021, FDA approved Xywav for the treatment of IH in adults. Xywav is the first and only FDA-approved therapy to treat IH. We initiated the U.S. commercial launch of Xywav for the treatment of IH in adults on November 1, 2021. IH is a debilitating neurologic sleep disorder characterized by chronic EDS (the inability to stay awake and alert during the day resulting in the irrepressible need to sleep or unplanned lapses into sleep or drowsiness), severe sleep inertia, and prolonged and non-restorative nighttime sleep. Although there are overlapping clinical features with other conditions, including narcolepsy, IH has its own specific diagnostic criteria. IH can significantly affect social, educational and occupational functioning. An estimated 37,000 people in the U.S. have been diagnosed with IH and are actively seeking healthcare. In January 2022, FDA recognized seven years of ODE for Xywav in IH through August 12, 2028.

In 2021, net product sales of Xywav were $535.3 million, which represented 17% of our total net product sales. There were approximately 6,900 active patients on Xywav exiting the fourth quarter of 2021, including approximately 6,650 active patients with narcolepsy and approximately 250 active patients with IH. With respect to Xywav and Xyrem in the aggregate, the average number of active oxybate patients on therapy was approximately 16,200 in the fourth quarter of 2021.

Xyrem. Xyrem is a product approved by FDA and distributed in the U.S. for the treatment of both cataplexy and EDS in both adult and pediatric patients with narcolepsy. Sodium oxybate, the active pharmaceutical ingredient, or API, in Xyrem, is a formulation of the sodium salt of gamma-hydroxybutyrate, an endogenous neurotransmitter and metabolite of gamma-aminobutyric acid.

Xyrem was approved in the U.S. for the treatment of cataplexy in adult patients with narcolepsy in 2002 and was approved for EDS in adult patients with narcolepsy in 2005. In October 2018, Xyrem was also approved in the U.S. for the treatment of cataplexy or EDS in pediatric narcolepsy patients ages seven and older. In its updated 2021 treatment guidelines, the American Academy of Sleep Medicine gives sodium oxybate a strong recommendation for the treatment of narcolepsy in adults. To support the development and commercialization of Xyrem internationally, we have license and distribution agreement with UCB Pharma Limited, or UCB, across other countries. This agreement provides UCB and its affiliates with the sole right to commercialize Xyrem in exclusive territories for all indications.

In 2021, net product sales of Xyrem were $1.3 billion, which represented 41% of our total net product sales.

Xywav and Xyrem REMS. Our marketing, sales and distribution of Xywav and Xyrem in the U.S. are subject to a REMS, which is required by FDA to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, abuse, misuse and diversion of Xywav and Xyrem. Under this REMS, all of the Xywav and Xyrem sold in the U.S. must be dispensed and shipped directly to patients or caregivers through a central pharmacy. Xywav and Xyrem may not be stocked in retail pharmacies. Physicians and patients must complete an enrollment process prior to fulfillment of Xywav and Xyrem prescriptions, and each physician and patient must receive materials concerning the serious risks associated with Xywav and Xyrem before the physician can prescribe, or a patient can receive, the product. The central certified pharmacy must monitor and report instances of patient or prescriber behavior giving rise to a reasonable suspicion of abuse, misuse or diversion of Xywav and Xyrem, and maintains enrollment and prescription monitoring information in a central database. The central pharmacy ships the product directly to the patient (or caregiver) by a courier service.

We have had exclusive agreements with Express Scripts Specialty Distribution Services, Inc., or ESSDS, the central pharmacy for Xywav and Xyrem, to distribute Xywav and Xyrem in the U.S. and provide patient support services related to Xyrem since 2002. In July 2020, upon expiration of the existing exclusive agreements with ESSDS, we entered into new agreements with ESSDS with a two-year term. Our current agreements with ESSDS, which expire on July 1, 2022, may be terminated by either party at any time without cause on 180 days' prior written notice to the other party.

Epidiolex. We acquired Epidiolex (Epidyolex outside the U.S.) in May 2021 as part of the GW Acquisition, which expands our growing neuroscience business with a global, high-growth childhood-onset epilepsy franchise. Epidiolex is a pharmaceutical formulation comprising highly purified plant-derived cannabidiol, or CBD, for which we retain global commercial rights. Epidiolex was approved in the U.S. in June 2018 for the treatment of seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome, or LGS, and Dravet syndrome, or DS, in patients two years of age and older, and subsequently approved in July 2020 for the treatment of seizures associated with tuberous sclerosis complex, or TSC, in patients one year of age and older. FDA also approved the expansion of the prior approved indications, LGS and DS, to patients one year of age and older. The rolling European launch of Epidyolex is also underway following European Commission, or EC, approval in September 2019 for use as adjunctive therapy of seizures associated with LGS or DS, in conjunction with clobazam, for patients two years of age and older. The clobazam restriction is limited to EU and Great Britain. Outside the U.S. and Europe, Epidiolex/Epidyolex is approved in Israel and Australia. See "Research and Development" below for a discussion of clinical development activities for Epidiolex.

LGS and DS are severe childhood-onset, drug-resistant epilepsy syndromes. LGS and DS affect approximately 35,000-50,000 and approximately 10,000 individuals in the U.S., respectively. TSC is a rare genetic disorder that causes non-malignant tumors to form in many different organs and is a leading cause of genetic epilepsy. TSC affects approximately 50,000 individuals in the U.S. Epidiolex has received ODE to treat seizures associated with LGS and DS through 2025 and TSC through 2027.

Net product sales of Epidiolex/Epidyolex in 2021, beginning from the closing of the GW Acquisition on May 5, 2021 were $463.6 million, which represented 15% of our total net product sales. On a pro forma basis, assuming the GW Acquisition had closed on January 1, 2021, Epidiolex/Epidyolex net product sales in 2021 were $658.3 million. For a detailed discussion of the GW Acquisition, see "Management's Discussion and Analysis of Financial Condition and Results of Operations" in Part II, Item 7 of this Annual Report on Form 10-K.

Sunosi. Sunosi received FDA approval in March 2019 and was launched in the U.S. in July 2019 to improve wakefulness in adult patients with EDS associated with narcolepsy or OSA. Sunosi was also approved in January 2020 by the EC to improve wakefulness and reduce EDS in adults with narcolepsy (with or without cataplexy) or OSA. We launched Sunosi in Germany for the treatment of narcolepsy in May 2020 followed by OSA in July 2021 and for the treatment of both indications in Denmark in October 2020, in France in March 2021, and in Italy in April 2021. We expect to continue the rolling launch in Europe as we secure pricing and reimbursement approvals in more European countries. Sunosi was approved in Canada in May 2021 for the treatment of EDS associated with narcolepsy or OSA in adult patients.

OSA, commonly referred to as sleep apnea, is a highly prevalent disease, and EDS, a major symptom of OSA, is characterized by the inability to stay awake and alert during the day resulting in unplanned lapses into sleep or drowsiness. Although positive airway pressure therapy, with its most common form being continuous positive airway pressure, or CPAP, has been shown to be an effective therapy for sleep apnea that frequently results in improvement in EDS in many patients, not all patients tolerate CPAP therapy and among those who tolerate CPAP, usage is highly variable. EDS may persist in people with OSA despite using CPAP.

In 2021, net product sales of Sunosi were $57.9 million, which represented 2% of our total net product sales.

Sativex. We acquired Sativex (nabiximols) in May 2021 as part of the GW Acquisition. Sativex is approved in the U.K. and certain other countries outside the U.S. as treatment for symptom improvement in adult patients with moderate to severe spasticity due to MS, who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy.

Nabiximols is a complex botanical mixture formulated from extracts of the cannabis sativa plant that contains the principal cannabinoids delta-9-tetrahydrocannabinol, or THC, and CBD as well as specific minor cannabinoids and other non-cannabinoid components. We developed nabiximols to be administered as an oromucosal spray, whereby the active ingredients are absorbed in part in the lining of the mouth, either under the tongue or inside the cheek. Nabiximols is already approved in more than 25 countries outside the U.S. for the treatment of spasticity due to multiple sclerosis under the brand name Sativex. We market Sativex directly in the U.K. To support the development and commercialization of Sativex internationally, we have license and development agreements with commercial partners across other countries. These agreements provide our collaborators with the sole right to commercialize Sativex in exclusive territories for all indications. See "Research and Development" below for a discussion of clinical development activities for nabiximols.

Net product sales of Sativex in 2021, beginning from the closing of the GW Acquisition on May 5, 2021 were $12.7 million, which represented less than 1% of our total net product sales. On a pro forma basis, assuming the GW Acquisition had closed on January 1, 2021, Sativex net product sales in 2021 were $18.5 million.

Oncology

Zepzelca. In December 2019, we entered into an exclusive license agreement with Pharma Mar, S.A., or PharmaMar, pursuant to which we obtained exclusive U.S. development and commercialization rights to Zepzelca. In October 2020, we entered into an amendment to the license agreement with PharmaMar to expand our exclusive license to include rights to develop and commercialize Zepzelca in Canada. The term of the amended license agreement extends on a licensed product-by-licensed product and country-by-country basis until the latest of: (i) expiration of the last PharmaMar patent covering Zepzelca in that country (subject to certain exclusions), (ii) expiration of regulatory exclusivity for Zepzelca in that country and (iii) 12 years after the first commercial sale of Zepzelca in that country. We have the right to terminate the amended license agreement at will upon a specified notice period, and either party can terminate the amended license agreement for the other party's uncured material breach or bankruptcy. For a description of additional terms of the amended license agreement, including financial terms, see Note 3, Business Combinations, Asset Acquisitions and Collaborations—License Agreement of the Notes to Consolidated Financial Statements included in Part IV of this Annual Report on Form 10-K.

Zepzelca for injection (4 mg) is approved by FDA to treat adults with metastatic SCLC, with disease progression on or after platinum-based chemotherapy. Zepzelca is an alkylating drug that binds guanine residues within DNA. This triggers a cascade of events that can affect the activity of DNA binding proteins, including some transcription factors, and DNA repair pathways, resulting in disruption of the cell cycle and eventual cell death. Zepzelca was granted Orphan Drug Designation for SCLC by FDA in August 2018. In December 2019, PharmaMar submitted a New Drug Application, or NDA, to FDA for accelerated approval of Zepzelca for relapsed SCLC based on data from a Phase 2 trial, and in February 2020, FDA accepted the NDA for filing with priority review. In June 2020, FDA granted accelerated approval of Zepzelca for the treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy. Zepzelca is approved based on response rate and duration of response. After discussion with FDA, PharmaMar initiated a confirmatory trial in second-line SCLC in December 2021. This is a three-arm trial comparing Zepzelca as either monotherapy or in combination with irinotecan to investigator's choice of irinotecan or topotecan. Data from this trial, if positive, will serve as the confirmatory trial for Zepzelca to secure full approval in the U.S. See "Research and Development" below for a discussion of clinical development activities for Zepzelca.

In 2021, net product sales of Zepzelca were $246.8 million, which represented 8% of our total net product sales.

Rylaze. Rylaze was approved by FDA in June 2021 under the Real-Time Oncology Review (RTOR) program, and was launched in the U.S. in July 2021, for use as a component of a multi-agent chemotherapeutic regimen for the treatment of ALL or LBL in pediatric and adult patients one month and older who have developed hypersensitivity to *E. coli*-derived asparaginase. Rylaze is the only recombinant *erwinia* asparaginase manufactured product that maintains a clinically meaningful level of serum asparaginase activity throughout the entire intended duration of treatment. We developed Rylaze with the goal of addressing the needs of patients and health care providers for an innovative, high-quality *erwinia* asparaginase with reliable supply. Rylaze has been granted Orphan Drug Designation for the treatment of patients with ALL or LBL. See "Research and Development" below for a discussion of clinical development activities for Rylaze.

In 2021, net product sales of Rylaze were $85.6 million, which represented 3% of our total net product sales.

Vyxeos. Vyxeos is a liposomal formulation of a fixed ratio combination of daunorubicin and cytarabine for intravenous infusion that is indicated for the treatment of adults with newly-diagnosed t-AML or AML-MRC and has been shown to have synergistic effects at killing leukemia cells in vitro and in animal models. Vyxeos is the first drug delivery combination product based on our CombiPlex® technology platform to be approved by FDA and the EC.

AML is a rapidly progressing and life-threatening blood cancer that begins in the bone marrow, which produces most of the body's new blood cells. AML cells crowd out healthy cells and move aggressively into the bloodstream to spread cancer to other parts of the body. AML is a relatively rare disease representing about 1% of all new cancer cases and has the lowest survival rate of any form of leukemia. Patients with newly diagnosed t-AML or AML-MRC may have a particularly poor prognosis.

In 2017, we launched Vyxeos in the U.S. after FDA approved our NDA for the treatment of adults with newly-diagnosed t-AML or AML-MRC. In August 2018, the EC granted marketing authorization for Vyxeos and, as part of our rolling launch of Vyxeos in Europe, we are continuing to make pricing and reimbursement submissions in European countries.

In March 2021, FDA approved a revised label to include a new indication to treat newly-diagnosed t-AML or AML with myelodysplasia-related changes in pediatric patients aged one year and older. We have a number of ongoing development activities and continue to expand into new markets internationally. See "Research and Development" below for a discussion of clinical development activities for Vyxeos.

In 2021, Vyxeos product sales were $134.1 million, which represented 4% of our total net product sales.

Defitelio. Defibrotide, the API in Defitelio, is approved for the treatment of VOD, a potentially life-threatening complication of HSCT, and is in development for other complications following anti-cancer treatment. Defibrotide is the sodium salt of a complex mixture of single-stranded oligodeoxyribonucleotides derived from porcine DNA. Defibrotide mediates its effects via interaction with endothelial cells. Non-clinical data suggest that defibrotide stabilizes endothelial cells by reducing endothelial cell activation and by protecting them from further damage.

Stem cell transplantation is a frequently used treatment modality for hematologic cancers and other conditions in both adults and children. Certain conditioning regimens used as part of HSCT can damage the cells that line the hepatic vessels, which is thought to lead to the development of VOD, also referred to as SOS, a blockage of the small vessels in the liver, that can lead to liver failure and potentially result in significant dysfunction in other organs such as the kidneys and lungs. Severe VOD is the most extreme form of VOD and is associated with multi-organ failure and high rates of morbidity and mortality. An analysis of retrospective data, prospective cohort studies and clinical trials published between 1979 and 2007 found that the 100-day mortality rate in severe VOD cases is greater than 80%.

The EC granted marketing authorization under exceptional circumstances for Defitelio for the treatment of severe VOD in adults and children undergoing HSCT in 2013. We commenced a rolling launch of Defitelio in European countries in 2014.

In 2016, FDA approved our NDA for Defitelio for the treatment of adult and pediatric patients with VOD with renal or pulmonary dysfunction following HSCT. We launched Defitelio in the U.S. shortly after FDA approval. We also launched defibrotide in Canada in 2017. In June 2019, Nippon Shinyaku Co., Ltd., the partner to whom we have granted exclusive rights to develop and commercialize defibrotide in Japan, received marketing authorization from Japan's Ministry of Health, Labour and Welfare and launched defibrotide in Japan in September 2019. Further geographic expansion occurred in July 2020 and September 2020, as Defitelio was approved by the Australian Therapeutic Goods Administration and Swissmedic in Switzerland, respectively, for the treatment of VOD.

In 2021, Defitelio/defibrotide product sales were $197.9 million, which represented 6% of our total net product sales.

Revenue Diversification

As part of our objective to reduce business risk by diversifying our revenue sources, we have been actively seeking to expand our commercial portfolio thorough a combination of launching internally developed therapies and corporate development. In 2018, 75% of net product sales were generated by one product, Xyrem. In the fourth quarter of 2021, 59% of net product sales were generated from products that we launched or acquired since 2019, including Xywav, Zepzelca, Epidiolex, Sunosi, Sativex and Rylaze.

Product	Indication(s)	Initial Approval Date	Market(s)
NEUROSCIENCE			
Xywav® (calcium, magnesium, potassium, and sodium oxybates)	Treatment of cataplexy or EDS in patients seven years of age and older with narcolepsy.	July 2020	U.S.
	Treatment of IH in adults.	August 2021	U.S.
Xyrem® (sodium oxybate)	Treatment of cataplexy or EDS in patients seven years of age and older with narcolepsy.	July 2002	U.S.
	For the treatment of cataplexy in patients with narcolepsy.	August 2005	Canada
	Treatment of narcolepsy with cataplexy in adult patients, adolescents and children from age of 7 years.	October 2005	EU, Great Britain, other markets (through licensing agreement)

Epidiolex® (cannabidiol)	Treatment of seizures associated with LGS, DS or TSC, in patients 1 year of age and older.	June 2018	U.S.
	For adjunctive therapy of seizures associated with LGS or DS, in conjunction with clobazam, for patients 2 years of age and older.*	September 2019	EU, Great Britain, other markets
Epidyolex® (cannabidiol)	For adjunctive therapy of seizures associated with TSC for patients 2 years of age and older.**	April 2021	EU, Great Britain, other markets
Sunosi® (solriamfetol)	Improve wakefulness in adult patients with EDS associated with narcolepsy or OSA.	March 2019	U.S.
	Improve wakefulness and reduce EDS in adult patients with narcolepsy (with or without cataplexy) or adult patients with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as CPAP.	January 2020	EU, Great Britain
	Treatment of EDS in adult patients with narcolepsy or OSA.	May 2021	Canada
Sativex® (nabiximols)	Treatment for adult patients with moderate to severe spasticity due to MS, who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.	June 2010	U.K. and Canada (other markets through licensing agreements with partners)
ONCOLOGY			
Zepzelca® (lurbinectedin)	Treatment of adult patients with metastatic SCLC, with disease progression on or after platinum-based chemotherapy.	June 2020	U.S. (licensed from PharmaMar)
	Treatment of adults with Stage III or metastatic SCLC who have progressed on or after platinum-containing therapy.	September 2021	Canada (licensed from PharmaMar)
Rylaze™ (asparaginase erwinia chrysanthemi (recombinant)-rywn)	A component of a multi-agent chemotherapeutic regimen for the treatment of ALL, and LBL, in adult and pediatric patients 1 month or older who have developed hypersensitivity to *E. coli*-derived asparaginase.	June 2021	U.S.

Vyxeos® (daunorubicin and cytarabine) liposome for injection	Treatment of newly-diagnosed therapy-related t-AML or AML-MRC in adults and pediatric patients one year and older.	August 2017	U.S.
Vyxeos® liposomal 44 mg/100 mg powder for concentrate for solution for infusion	Treatment of adults with newly-diagnosed t-AML or AML-MRC.	August 2018	EU, Great Britain
Vyxeos® Daunorubicin and cytarabine liposome for injection Powder, 44 mg daunorubicin and 100 mg cytarabine per vial, intravenous infusion	Treatment of adults with newly diagnosed therapy-related t-AML or AML with AML-MRC.	April 2021	Canada
Defitelio® (defibrotide sodium)	Treatment of adult and pediatric patients with hepatic VOD, also known as SOS, with renal or pulmonary dysfunction following HSCT.	March 2016	U.S.
Defitelio® (defibrotide)	Treatment of severe hepatic VOD, also known as SOS, following HSCT therapy.	October 2013	EU, Great Britain, other markets

*The Clobazam restriction limited to EU and Great Britain

**TSC approval pending in certain markets

Research and Development

A key aspect of our strategy is our continued investment in expanding our research and development organization and initiatives. We actively explore new options for patients including novel compounds, small molecule advancements, biologics and innovative delivery technologies. We are focused on research and development activities within our neuroscience and oncology therapeutic areas, such as our expansion into movement disorders and solid tumors, and exploring and potentially investing in adjacent therapeutic areas.

Our development activities encompass all stages of development and currently include clinical testing of new product candidates and activities related to clinical improvements of, or additional indications or new clinical data for, our existing marketed products. We also have active preclinical programs for novel therapies, including precision medicines in hematology and oncology and the GW cannabinoid platform. We are increasingly leveraging our growing internal research and development function, and we have also entered into collaborations with third parties for the research and development of innovative early-stage product candidates and have supported additional investigator-sponsored trials, or ISTs, that are anticipated to generate additional data related to our products. We also seek out investment opportunities in support of development of early- and mid-stage technologies in our therapeutic areas and adjacencies. We have a number of licensing and collaboration agreements with third parties, including biotechnology companies, academic institutions and research-based companies and institutions, related to preclinical and clinical research and development activities in hematology and in precision oncology, as well as in neuroscience.

Our current and planned development activities in our neuroscience therapeutic area are focused on an additional indication for Epidiolex, and advancing novel therapies, including nabiximols, suvecaltamide (JZP385) and JZP150.

Epidiolex. We anticipate the initiation of a pivotal Phase 3 clinical trial of Epidiolex for the treatment of Epilepsy with Myoclonic-Atonic Seizures, or EMAS, also known as Doose syndrome, in the first half of 2022. This trial is designed to evaluate Epidiolex in a fourth childhood-onset epileptic encephalopathy with high unmet need. EMAS is characterized by generalized myoclonic-atonic seizures, and this trial is designed to provide the first randomized, controlled clinical data with Epidiolex in this syndrome type. Seizure types including atonic, tonic, clonic, tonic-clonic, and partial onset seizures are seen in LGS, DS and TSC.

Nabiximols. We have three ongoing Phase 3 clinical trials in multiple sclerosis (MS)-related spasticity. Collectively these trials will expand the body of evidence on the safety and efficacy of nabiximols in addressing spasticity in MS patients, and either individually or jointly may support an NDA submission to FDA. Spasticity occurs in up to 84% of MS patients, and approximately one-third of those who experience spasticity live with uncontrolled symptoms. The first trial is a smaller, shorter trial relative to the other two. The first trial is assessing changes in muscle tone using elements of the Modified Ashworth scale.

If results from this first trial are positive, there is the potential for an NDA submission to FDA by the end of 2022. The two additional trials have larger sample sizes.

Suvecaltamide. Suvecaltamide (JZP385) is a highly selective modulator of T-type calcium channels currently in development for the treatment of essential tremor, or ET. ET is the most common pathological movement disorder, and there have been no new approved therapies in more than 50 years. We acquired suvecaltamide in our acquisition of Cavion, Inc., or Cavion, a clinical-stage biotechnology company, in August 2019. We initiated a Phase 2b clinical trial of suvecaltamide in December 2021. In this multicenter, double-blind, randomized, placebo-controlled trial, we are evaluating the safety and efficacy of suvecaltamide in the treatment of adults with moderate to severe ET. The primary efficacy outcome measure is the change from baseline to Week 12 on the Tremor Research Group Essential Tremor Rating Assessment Scale (TETRAS) composite outcome score, which represents items from the TETRAS-Activities of Daily Living and TETRAS-Performance Subscale, and measures the functional impact due to tremor.

JZP150. JZP150 is a fatty acid amide hydrolase, or FAAH, inhibitor program for the potential treatment of post-traumatic stress disorder, or PTSD, and associated symptoms. PTSD affects up to 8% of adults during their lifetime, and there are limited treatment options available. In October 2020, we entered into an asset purchase and exclusive license agreement with SpringWorks, under which we acquired SpringWorks' FAAH inhibitor program, including an assignment of SpringWorks' proprietary FAAH inhibitor PF-04457845, or PF-'845, now named JZP150. We initiated a Phase 2 clinical trial of JZP150 for PTSD in December 2021. In this trial, we are evaluating the safety and efficacy of JZP150 in the treatment of adults with PTSD as measured by improvement in the Clinician Administered Post Traumatic Stress Disorder (PTSD) Scale (CAPS-5) Total Symptom Severity Score, a validated clinical instrument for assessing the severity of PTSD symptoms.

Our current and planned research and development activities in our oncology therapeutic area are focused on Rylaze and Zepzelca, including in combination with other therapeutic agents, exploring additional indications for Vyxeos, and the research and development of new product candidates through our external collaborations.

Zepzelca. In collaboration with F. Hoffmann-La Roche Ltd, or Roche, we have initiated a Phase 3 pivotal clinical trial in first-line extensive stage SCLC of Zepzelca in combination with Tecentriq® (atezolizumab). After discussion with FDA, our licensor PharmaMar initiated a confirmatory trial in second-line SCLC in December 2021. This is a three-arm trial comparing Zepzelca as either monotherapy or in combination with irinotecan to investigator's choice of irinotecan or topotecan. Data from this trial, if positive, would serve as the confirmatory trial for Zepzelca to secure full approval in the U.S.

We initiated a Phase 2 basket trial in the first quarter of 2022 to explore Zepzelca monotherapy in patients with select advanced or metastatic solid tumors. Cohorts will include advanced urothelial cancer, large cell neuroendocrine tumor of the lung, and homologous recombinant deficient positive (HRD+) cancers. In addition, we have initiated a Phase 4 observational study to collect real world safety and outcome data in adult Zepzelca monotherapy patients with SCLC who progress on or after prior platinum-containing chemotherapy.

Rylaze. The current approved recommended dosage of Rylaze is for an intramuscular, or IM, administration of 25 mg/m^2 every 48 hours. In February 2022, we announced the submission of a supplemental Biologics License Application, or sBLA, to FDA with data to support a Monday/Wednesday/Friday (M/W/F) IM dosing schedule, which has also been granted review under the RTOR program. An additional part of the ongoing Rylaze study has evaluated intravenous, or IV, administration and, if the data are supportive, we expect to submit an additional sBLA to FDA in 2022 in support of IV administration. We also are planning a regulatory submission in Europe for IM and IV administration in mid-2022.

Vyxeos. Our Vyxeos clinical development strategy is designed to target potential new patient segments across the AML landscape and to generate clinical data on Vyxeos when used in combination with other therapeutic agents. As reflected in the table below, we are pursuing this strategy by sponsoring clinical trials, working with cooperative groups who are conducting clinical trials, and partnering with The University of Texas MD Anderson Cancer Center, or MD Anderson. In August 2018, we announced a five-year collaboration with MD Anderson to evaluate potential treatment options for hematologic malignancies, with a near-term focus on Vyxeos, and shortly thereafter, commenced development activities under this collaboration. In addition, there are multiple ongoing ISTs studying Vyxeos.

CombiPlex Platform. We are also evaluating the use of our CombiPlex delivery technology platform in a number of therapeutic formulations and combinations in oncology as part of our internal oncology research and development activities. CombiPlex enables the design and rapid evaluation of various combinations of therapies to deliver enhanced anti-cancer activity by identifying an optimal synergistic ratio of drugs in vitro and fixing this ratio in a nanoscale delivery complex that maintains and then coordinates the release of the synergistic combination after administration. CombiPlex utilizes two proprietary nanoscale delivery platforms: liposomes to control the release and distribution of water-soluble drugs and drugs that are both water- and fat-soluble (amphipathic), and nanoparticles to control the release and distribution of non-water-soluble (hydrophobic) drugs.

Through third parties, we are also pursuing preclinical and clinical research and development activities in hematology and in precision oncology under a number of licensing and collaboration agreements, including with:

- Codiak BioSciences, Inc., or Codiak, for an exclusive, worldwide, royalty-bearing license to develop, manufacture and commercialize potential therapeutic candidates directed at up to four targets to be developed using Codiak's engEx™ precision engineering platform for exosome therapeutics;
- Pfenex, Inc., which was acquired by Ligand Pharmaceuticals Incorporated, or Ligand, for rights to JZP341, an early-stage long-acting *Erwinia* asparaginase;
- XL-protein GmbH, or XLp, for rights to use XLp's PASylation® technology to extend the plasma half-life of selected asparaginase product candidates; and
- Redx Pharma, or Redx, for preclinical collaboration activities related to the pan-Raf inhibitor program that we purchased from Redx for the potential treatment of Raf and Ras mutant tumors and to discover and develop drug candidates for two cancer targets in the Ras/Raf/MAP kinase pathway.

Below is a summary of our key ongoing and planned development projects related to our products and pipeline and their corresponding current stages of development:

Product Candidates	**Description**
NEUROSCIENCE	
Phase 3	
Epidiolex	EMAS, also known as Doose syndrome (planned study)
Nabiximols	MS Spasticity (multiple studies ongoing) Spinal cord injury spasticity (planned study)
Phase 2b	
Suvecaltamide (JZP385)	ET (ongoing study)
Phase 2	
JZP150	PTSD (ongoing study)
Additional cannabinoids	Schizophrenia (ongoing study) Autism spectrum disorders (ongoing study)
Phase 1	
JZP324	Oxybate extended-release formulation (planned study)
Additional cannabinoids	Neonatal hypoxic-ischemic encephalopathy (ongoing study) Neuropsychiatry targets (ongoing study)
Preclinical	
Undisclosed targets	Neuroscience Cannabinoids
ONCOLOGY	
Regulatory Review	
Rylaze	ALL/LBL FDA approval in June 2021; announced completion of sBLA submission to FDA in January seeking approval for Monday/Wednesday/Friday intramuscular dosing schedule; regulatory submission planned for Europe in mid-2022
Phase 3	
Zepzelca	First-line extensive stage SCLC in combination with Tecentriq (collaboration with Roche) (ongoing study) Confirmatory Study (Pharma Mar study) (ongoing study)
Vyxeos	AML or high-risk Myelodysplastic Syndrome, or MDS (AML18) (cooperative group studies) (ongoing study) Newly diagnosed adults with standard- and high-risk AML (AML Study Group cooperative group study) (ongoing study) Newly diagnosed pediatric patients with AML (Children's Oncology Group cooperative group study) (ongoing study)
Phase 2	
Zepzelca	Basket trial including urothelial cancer, large cell neuroendocrine tumor of the lung, and HRD+ (homologous recombinant deficient) cancers (ongoing study)

Vyxeos	High-risk MDS (European Myelodysplastic Syndromes Cooperative Group cooperative group study) (ongoing study) Newly diagnosed older adults with high-risk AML (cooperative group study) (planned study)
Vyxeos + venetoclax	De novo or relapsed/refractory, or R/R, AML (MD Anderson collaboration study) (ongoing study)
Phase 1	
Vyxeos	Low intensity dosing for higher risk MDS (MD Anderson collaboration study) (ongoing study)
Vyxeos + other approved therapies	R/R AML or hypomethylating agent failure MDS (MD Anderson collaboration study) (ongoing study) First-line, fit AML (Phase 1b study) (ongoing study) Low intensity therapy for first-line, unfit AML (Phase 1b study) (ongoing study)
Preclinical	
CombiPlex®	Hematology/oncology exploratory activities
JZP341 (long-acting *Erwinia* asparaginase)	ALL and other hematological malignancies (collaboration with Ligand)
Pan-Raf inhibitor program	Raf and Ras mutant tumors (acquired from Redx, which is continuing development)
Undisclosed targets	Ras/Raf/MAP kinase pathway (collaboration with Redx) Oncology
Exosome targets (up to 4)	Hematological malignancies/solid tumors (collaboration with Codiak BioSciences, Inc., or Codiak)
Undisclosed targets	Oncology

As a result of the effects of the COVID-19 pandemic, we have taken measures to implement remote and virtual approaches, including remote data monitoring where possible, to maintain patient safety and trial continuity and to preserve study integrity. For a more detailed discussion of the impact of the COVID-19 pandemic on our clinical trial activities, see “Management’s Discussion and Analysis of Financial Condition and Results of Operations—Overview—COVID-19 Business Update” in Part II, Item 7 of this Annual Report on Form 10-K and “Risk Factors” in Part I, Item 1A of this Annual Report on Form 10-K.

Commercialization Activities

We have commercial operations primarily in the U.S., Europe and Canada. In the U.S., our products are commercialized through a number of teams, including a team of experienced, trained sales professionals who provide education and promote Xywav, Xyrem, Epidiolex, Sunosi, Zepzelca, Rylaze, Vyxeos and Defitelio to healthcare providers in the appropriate specialties for each product, a team that interacts with payors and institutions to ensure access and coverage for the products, and a team that distributes the products throughout the U.S. healthcare system (wholesalers, pharmacies, hospitals, and community and academic institutions) and provides patient services.

In Canada and in approved markets in Europe where we commercialize Defitelio and Vyxeos, we have a field force of hematology sales specialists. In markets where these products either are not approved or are unable to be promoted under local regulation, we have medical affairs personnel responsible for responding to medical information requests and for providing information consistent with local treatment protocols with respect to such products. In certain European markets, we have a sales team and a team of medical science liaisons supporting our rolling launches of Epidyolex and Sunosi. Outside the U.S., we directly market Xyrem, Sunosi and Zepzelca in Canada. We also utilize distributors in certain markets outside the U.S. where we do not market our products directly.

Other commercial activities include marketing related services, industry analytics and insights, distribution services and commercial support services. We employ third party vendors, such as advertising agencies, market research firms and suppliers of marketing and other sales support-related services, to assist with our commercial activities. We also provide reimbursement support for our U.S. markets.

We intend to scale the size of our sales force as appropriate to effectively reach our target audience in the specialty markets in which we currently operate. We promote Zepzelca, Rylaze, Vyxeos and Defitelio to many hematology and oncology specialists who operate in the same hospitals and outpatient clinical sites, and we believe that we benefit from operational synergies from this overlap. We expect that a potential launch of Rylaze in Europe would require minimal additional support. Continued growth of our current marketed products and the launch of any future products may require a

reevaluation of our field force and support organization in and outside the U.S. In addition, beginning in March 2020, we transitioned our field-based sales, market access, reimbursement and medical employees out of the field and suspended work-related travel and in-person customer interactions as a result of the COVID-19 pandemic. We utilized technology to continue to engage healthcare professionals and other customers virtually to support patient care. In late June 2020, as clinics and institutions began to allow in-person interactions pursuant to local health authority and government guidelines, our field teams resumed in-person interactions with healthcare professionals and clinics combined with virtual engagement. The level of renewed engagement varies by account, region and country. There continues to be some negative impact on demand, new patient starts and treatments for our products arising from the pandemic, primarily due to the inherent limitations of telemedicine and a reprioritization of healthcare resources toward COVID-19. As healthcare systems have adapted to cope with the ongoing situation, we have seen improvements. The lack of access to health care providers has caused, and may continue to cause, delays in appropriate diagnosis, treatment and ongoing care for some patients, which could subsequently impact prescribing and use of our products. For a more detailed discussion of the impact of the COVID-19 pandemic on our commercialization activities, see “Management’s Discussion and Analysis of Financial Condition and Results of Operations—Overview—COVID-19 Business Update” in Part II, Item 7 of this Annual Report on Form 10-K.

Human Capital Management and Environment, Health and Safety

Jazz is committed to creating a company where the culture embodies our corporate purpose to innovate to transform the lives of patients and reflects our key goals: (1) be a great place to work; and (2) live our core values of *Integrity, Collaboration, Passion, Innovation, and Pursuit of Excellence.*

Employee Demographics. As of February 22, 2022, Jazz employed approximately 3,200 people worldwide, of which approximately 50% were employed in the U.S. and approximately 50% were outside the U.S. primarily in the U.K., Ireland and across the European Union, or EU. As an innovative biopharmaceutical company, we have over 700 full-time employees — greater than 22% of our global workforce — supporting our research and development activities. We consider our employee relations to be very good.

Diversity, Equity, Inclusion and Belonging. We make diversity, equity, inclusion and belonging, or DEIB, a priority because it is a key to unlocking the potential of our people and living our core values.

We strive to create a workplace culture that fosters the ability of our employees to be their authentic selves and contribute boldly. We aspire to have multi-dimensional diversity through our entire Jazz workforce. We seek to surround underrepresented groups with allies to enable all employees to thrive equitably. Our Board and management team are committed to fostering DEIB in all parts of our business.

Our DEIB strategy includes: (1) building a more diverse workforce in terms of gender identity, race, ethnicity and sexual orientation and that represent unique backgrounds, experiences, thoughts and talents; (2) investing in developing our diverse talent and driving equity; and (3) and creating a culture of inclusion and belonging.

We designed our Employee DEIB program to empower employees to guide and support our strategy and programs related to hiring diverse talent and using education and communication to continue fostering an inclusive environment. We also have a DEIB Delegation, a committee of employees focused on helping to embed DEIB into all we do.

Jazz ConcERTos, our employee resource teams, are self-led teams of employee volunteers with diverse backgrounds who come together to promote innovation through inclusion and to increase awareness of all dimensions of diversity. We believe that these groups will contribute positively to Jazz’s culture and business success by working cross-functionally to drive innovation, helping to decrease unconscious bias, and encouraging employees to be their whole selves so they can perform at their best.

We have established goals related to increasing all dimensions of diversity, including representation of females and people of color, particularly at the leadership level (i.e., employees at executive director and above). In this regard, we have made some meaningful progress, as demonstrated by the following, as of February 9, 2022:

- 50% of each of our board of directors and Executive Committee is diverse in terms of gender, ethnicity and sexual orientation.
- Females represent 55% of our global workforce and 43% at the leadership level (employees at executive director and above).
- In the U.S., people of color represent 33% of our U.S. workforce and 20% at the leadership level.

While we are proud of what we have accomplished to date, we recognize there is still much to do. We remain committed to furthering our goals of providing a diverse, equitable and inclusive workplace that is supportive of all backgrounds, including among our broader leadership.

Employee Engagement. Jazz has a strong employee value proposition anchored in our shared commitment to our purpose to innovate to transform the lives of patients. We are committed to ensuring that we create a rich culture that provides a great place to work for our employees through company-wide efforts to connect employees to our shared purpose and to create an environment where our people feel valued, respected, and able to contribute to their full potential. We believe employee engagement and the power of our employee voices is foundational to strong performance. We have transparent and regular communication channels with our employees consisting of many forms – including all employee meetings, regular communication messages from executive leadership, top leadership forums, pulse check feedback mechanisms and engagement surveys.

Our employee feedback surveys are designed to help us measure overall employee engagement and we consistently achieve participation rates between 80 to 90% in our annual engagement survey. We consistently have high levels of engagement measured by feelings of connection to our mission, Jazz as a great place to work where their well-being is supported and they feel valued and included. It also provides important insight into the areas where we need to focus in the year ahead for several key components of our company objectives, such as decision-making, opportunities for development, and diversity, equity and inclusion. Our survey informs programs and activities aligned with achieving our corporate objectives and achieving our goal of evolving our operating culture for agility and scalability.

Our Community Beat teams are employee volunteers and representatives that promote company culture and create a sense of belonging and camaraderie among our employees. They foster programs and engagement activities on a local level to draw better connections to employees with the company strategy and business milestones, give back through community service, and promote different health and well-being initiatives.

Growth, Development and Total Rewards. Our talent strategy focuses on attracting the best talent, recognizing and rewarding the performance of our employees as defined by both *what* they accomplished and *how* they accomplished it, and continually developing our talent through new experiences and learning opportunities. We believe there is ample opportunity for growth and development at Jazz and there is not a one size fits all approach to growing our talent. We strive to create the best career experience for all of our employees. We work with each employee to chart their own course that matches their career ambitions and strengths with customized development.

Our performance management process supports our culture of continual feedback and coaching, and ongoing growth and development through new experiences and learning. We encourage all employees to have an individual development plan to outline learning and growth interests and focus areas.

We leverage several digital learning platforms to provide on demand bite sized learning to all employees that can be accessed 24/7 on a range of topics from leadership, personal effectiveness and well-being. We deliver our “Harmonize” program to all managers to ensure they are grounded in our core Leadership Behaviors we expect all leaders to demonstrate (Instills Trust, Values Differences, Executes through Teams, Develops Talent, Drives Accountability and Provides and Receives Feedback).

In 2021, we targeted a development effort towards our Global Leadership Team (top 70 leaders) and created a 9-month learning journey to build leadership excellence, strengthen relationships, and encourage cross functional collaboration in pursuit of our enterprise strategic goals. Additionally, we focused on diverse early career talent by piloting an executive coaching program to support their development. We offer tuition reimbursement in our major markets aimed at growth and career development.

Our management and leadership teams place significant focus and attention to diversity, capability development, and succession planning for critical roles. We regularly review talent development and succession plans for each of our functions to successfully maintain business operations and develop a pipeline of talent. We have goals concerning employee retention, diversity, and talent development.

We provide our employees with what we believe to be market competitive and locally relevant compensation and benefits that support our overarching strategy to attract, retain and reward highly talented employees in an extremely competitive and dynamic industry.

We strive to create a culture of health and well-being throughout the organization by offering a diverse and customizable set of programs focusing on employee experience, self-care, work-life balance, flexibility and early intervention. In addition to traditional employee benefits, Jazz supports employees and their families through access to a suite of innovative programs that are designed to enhance their physical, financial, emotional and social well-being. For 2022, we are introducing an enhanced suite of differentiated global leave and time-off polices to address the needs of our diverse employee population through varying stages of life, including minimum standards for new parent leave (irrespective of gender or how a family is created), family caregiver leave, and bereavement leave. Additionally, in 2022, we are launching a new global volunteer day, which will provide employees time off with full pay to give back to their communities.

Workplace Safety & Employee Care During COVID-19. Workplace safety is always a top priority for Jazz. To create and sustain a safe and healthy workplace, we have implemented initiatives designed to address risk evaluation, education and training of employees, use of appropriate personal protective equipment, and compliance with relevant national and international health and safety standards.

In response to COVID-19, we launched an employee support framework focused on Care, Connection, Continuity and Consciousness (our "4Cs") to enable our employees to live into our values and support one another while doing everything we can to deliver on our patient mission. Important to this framework were new leader expectations and tools given the rise and complexity of emerging employee demands and needs – including more flexibility to address personal needs, a greater connection to understand the whole person and their lives, and more active support surrounding social injustice. For example, we provided productivity and collaboration tools and resources for employees working remotely, including training and toolkits to help leaders effectively lead and manage remote teams; increased flexibility within work schedules and leave programs to support employees caring for children and others; expanded employees assistance and mindfulness programs to help employees and their families manage anxiety, stress, and overall wellbeing; and increased investment in resources focused on inclusion and belonging.

Environment, Health and Safety. Our operations are subject to complex and increasingly stringent environmental, health and safety laws and regulations in the countries where we operate and, in particular, in Ireland, the U.K. and Italy where we have manufacturing facilities. Our manufacturing activities involve the controlled storage, use and disposal of chemicals and solvents. Environmental and health and safety authorities in Ireland, the U.K. and Italy administer laws governing, among other matters, the emission of pollutants into the air (including the workplace), the discharge of pollutants into bodies of water, the storage, use, handling and disposal of hazardous substances, the exposure of persons to hazardous substances, and the general health, safety and welfare of employees and members of the public. In certain cases, such laws, directives and regulations may impose strict liability for pollution of the environment and contamination resulting from spills, disposals or other releases of hazardous substances or waste. Costs, damages and/or fines may result from the presence, investigation and remediation of such contamination at properties currently or formerly owned, leased or operated by us or at off-site locations, including where we have arranged for the disposal of hazardous substances or waste. In addition, we may be subject to third party claims, including for natural resource damages, personal injury and property damage, in connection with such contamination.

We seek to operate our manufacturing facilities in an environmentally responsible way to protect our people, our business, our environment and the local communities in which we operate. In light of the potential impact of our business on the environment, we have adopted a number of internal environmental policies and management systems designed to manage our operations in compliance with applicable laws, directives and regulations on environmental protection and in support of environmental sustainability and local biodiversity. Our environmental policies and management systems include procedures for assessing compliance with applicable environmental laws and regulations and reporting incidents of non-compliance to applicable governmental authorities. For example, we have environmental policies governing our manufacturing facilities in Ireland, the U.K. and Italy, which demonstrate our commitment to environmental sustainability and require us to minimize resource use (e.g., energy and water) and waste generation, optimize the use of raw materials, and undertake continuous improvement in environmental performance, with an emphasis on pollution prevention.

Competition

The biopharmaceutical industry is highly competitive. Our products compete, and our product candidates may in the future compete, with currently existing therapies, product candidates currently under development by us and others and/or future product candidates, including new chemical entities that may be safer, more effective or more convenient than our products. Any products that we develop may be commercialized in competitive markets, and our competitors, which include large global pharmaceutical companies and small research-based companies and institutions, may succeed in developing products that render our products obsolete or noncompetitive.

With respect to competition we face from generic drugs, certain U.S. state laws allow for, and in some instances in the absence of specific instructions from the prescribing physician mandate, the dispensing of generic products rather than branded products when a generic version is available. Generic competition often results in decreases in the prices at which branded products can be sold.

We are aware of: exploratory research into the effects of THC and CBD drug formulations; discovery research within the pharmaceutical industry into synthetic agonists and antagonists of CB1 and CB2 receptors; companies that supply synthetic cannabinoids and cannabis extracts to researchers for pre-clinical and clinical investigation; and various companies that cultivate cannabis plants with a view to supplying herbal cannabis or nonpharmaceutical cannabis-based formulations to patients. These activities have not been approved by the FDA but may in the future compete with our products.

In particular, our products and most advanced product candidates face or may face competition as described below:

- *Xywav and Xyrem*. While Xywav and Xyrem are currently the only products approved by FDA and marketed in the U.S. for the treatment of both cataplexy and EDS in both adult and pediatric patients with narcolepsy, we and others have launched products to treat EDS in narcolepsy and may in the future launch products to treat cataplexy in narcolepsy that are competitive with or disrupt the market. We expect to face competition from authorized generic and generic versions of sodium oxybate. For a description of generic versions of sodium oxybate and/or new products for the treatment of cataplexy and/or EDS that could compete with, or otherwise disrupt the market for, Xywav and Xyrem, as well as a description of our settlement agreements with abbreviated new drug application, or ANDA, filers, see the risk factor under the heading *"The introduction of new products in the U.S. market that compete with, or otherwise disrupt the market for, our oxybate products and product candidates would adversely affect sales of our oxybate products and product candidates"* in Part I, Item 1A of this Annual Report on Form 10-K.

  In addition to generic competition, Xywav and Xyrem may face competition in the future from other new sodium oxybate formulations for treatment of narcolepsy. In February 2021, FDA accepted for filing an NDA submitted by Avadel Pharmaceuticals plc, or Avadel, for an extended-release formulation of sodium oxybate which uses its proprietary technology for the treatment of EDS and cataplexy in patients with narcolepsy with a Prescription Drug User Fee Act, or PDUFA, target action date of October 15, 2021. On October 15, 2021, Avadel announced that FDA review is ongoing and FDA will likely not take action in October 2021 and will provide a new target action date. To obtain approval with ODE, Avadel will have to show clinical superiority to Xywav and Xyrem. We cannot predict the timing or approvability of Avadel's sodium oxybate product candidate or how FDA will evaluate any clinical superiority arguments that either we or Avadel may make, but in any event, we expect to face competition from Avadel, if its product candidate is approved.

  Xywav and Xyrem may also face increased competition from new branded entrants to treat EDS or cataplexy in narcolepsy such as pitolisant, which has been approved by FDA for the treatment of both cataplexy and EDS in adult patients with narcolepsy. Other companies have announced that they have product candidates in various phases of development to treat the symptoms of narcolepsy, such as Axsome Therapeutics, Inc.'s reboxetine, and various companies are performing research on orexin agonists for the treatment of sleep disorders.

  In addition, we are also aware that prescribers often prescribe branded or generic medications for cataplexy before prescribing or instead of prescribing oxybate therapy in Xywav or Xyrem, and that payors often require patients to try such medications before they will cover Xywav or Xyrem, even if they are not approved for this use. For example, prescribers often treat mild cataplexy with drugs that have not been approved by FDA for this indication, including tricyclic antidepressants and selective serotonin reuptake inhibitors or selective norepinephrine reuptake inhibitors. We are also aware that branded or generic stimulants may be prescribed off-label for treatment of EDS in narcolepsy. Wake-promoting agents modafinil and armodafinil, including both branded and generic equivalents, are approved for the treatment of EDS in narcolepsy and other conditions, and may be used in conjunction with or instead of Xywav or Xyrem.

- *Epidiolex.* Patients in the U.S. suffering from seizures associated with Dravet or LGS are treated with a variety of FDA-approved products, including clobazam, clonazepam, valproate, lamotrigine, levetiracetam, rufinamide, topiramate, ethosuximide, and zonisamide. FDA approved Zogenix, Inc.'s low-dose fenfluramine, or Fintepla, in DS in June 2020, and Zogenix submitted its supplemental NDA for LGS in 2021. In January 2022, Zogenix announced that it entered into a definitive agreement with UCB S.A. for the acquisition of Zogenix by UCB. Ovid Therapeutics Inc./Takeda Pharmaceutical Company Limited and Marinus Pharmaceuticals, Inc. are developing therapies for treating Developmental and Epileptic Encephalopathies (includes Dravet and LGS). Stiripentol has been approved in Europe for several years to treat DS and was approved in 2018 by the FDA. Zynerba Pharmaceuticals, Inc. is developing a topical formulation of CBD, for which it is working with FDA on a path forward on CONNECT-FX data for Zygel in Fragile X syndrome. There are a number of public and private companies in the early stages of developing genetic therapies for DS, including Stoke Therapeutics, Inc., which has an antisense oligonucleotide, STK-001, in early clinical trials.

- *Sunosi*. Sunosi faces competition from existing branded and generic products that treat EDS or improve wakefulness in adult patients with narcolepsy or OSA in a competitive retail pharmacy market. To successfully commercialize Sunosi, we need to differentiate Sunosi from other branded and generic products that treat EDS in patients with narcolepsy, including stimulants, wake-promoting agents, such as modafinil and armodafinil, and generic versions of stimulants and wake-promoting agents. We are also aware that stimulants are prescribed off-label for patients to treat excessive sleepiness in OSA. Sunosi faces competition from new branded entrants such as pitolisant, a drug that was approved by FDA in August 2019 for the treatment of EDS in adult patients with narcolepsy and in October 2020 for the treatment of cataplexy in adult patients with narcolepsy. Pitolisant became commercially available in the U.S. in the fourth quarter of 2019, and has also been approved and marketed in Europe to treat adult patients with narcolepsy,

with or without cataplexy, and OSA. Sunosi may also face competition from other products in development as potential treatments for EDS in patients with narcolepsy or OSA.

- *Nabiximols.* Nabiximols aims to treat adult patients with MS-related spasticity. Patients in the U.S. suffering from MS-related spasticity are currently treated with a variety of FDA-approved therapies such as baclofen, tizanidine, gabapentin, dantrolene and various botulinum toxin products. Bionorica SE is in late stage development of an oral solution containing dronabinol for spasticity due to MS. Ipsen and Echo pharmaceuticals are in the early stages of development with various oral products aimed to treat MS-related spasticity.
- *Zepzelca.* Zepzelca faces competition from topotecan, which is also an approved treatment in second line SCLC in the U.S., as well as other regimens for relapsed SCLC currently recommended in compendia guidelines. There are also a number of products and immunotherapies for the treatment of second line SCLC in various phases of development.
- *Rylaze.* Rylaze may face competition from Erwinase, which was previously approved and commercialized by Jazz as a treatment for ALL patients with hypersensitivity to *E. coli*-derived asparaginase. In April 2020, Porton Biopharma Limited, or PBL, granted Clinigen Group plc, or Clinigen, a global license for Erwinase. However, in December 2021, Clinigen announced that FDA has issued a Complete Response Letter to PBL's BLA for Erwinaze, indicating that the BLA cannot be approved in its current form. Rylaze may also face competition from other companies who have developed or are developing new treatments for ALL, including an L-asparaginase product candidate that is in development for the treatment of ALL patients. In addition, some new asparaginase treatments could reduce the rate of hypersensitivity in patients with ALL, and new treatment protocols are being developed and approved for ALL that may not include asparaginase-containing regimens, including some for the treatment of relapsed or refractory ALL patients. As a biologic product, Rylaze also faces potential competition from biosimilar products.
- *Vyxeos*. With respect to Vyxeos, there are a number of alternative established therapies in AML. A key consideration in the treatment of AML patients is the patient's suitability for chemotherapy. The AML patient population studied in the Vyxeos Phase 3 clinical trial supporting our NDA included 60-75 year old fit patients, or those deemed able to tolerate intensive induction chemotherapy. Prior to Vyxeos, the most widely recognized option for the treatment of newly-diagnosed t-AML and AML-MRC in fit patients was cytarabine in combination with daunorubicin, known as 7+3, which is still used today in this population, along with other intensive chemotherapy regimens, particularly in patients under the age of 60. Also, since Vyxeos was approved, several other products have been approved by FDA or are in development as treatment options for newly diagnosed AML patients eligible for intensive chemotherapy, such as targeted agents (e.g. midostaurin, enasidenib and ivosidenib), immunotherapies (e.g., gemtuzumab ozogamicin and chimeric antigen receptor T-cell therapy), and agents disrupting leukemia cell survival (e.g., glasdegib). We are also aware of the increasing use of venetoclax combined with either a hypomethylating agent or low-dose cytarabine, a treatment approved by FDA in newly diagnosed AML patients who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.
- *Defitelio*. While there is currently no direct competition to Defitelio to treat severe VOD, changes in the types of conditioning regimens used as part of HSCT may affect the incidence of VOD diagnosis and demand for Defitelio.

An important part of our corporate strategy is to build a diversified product pipeline, including by acquiring or in-licensing and developing, or partnering to license and develop, additional products and product candidates that we believe are highly differentiated and have significant commercial potential. Our ability to continue to grow our product portfolio requires that we compete successfully with other pharmaceutical companies, many of which may have substantially greater financial sales and marketing resources, to acquire or in-license products and product candidates.

Customers

In the U.S., Xywav and Xyrem are sold to one certified specialty pharmacy, ESSDS, that ships Xywav and Xyrem directly to patients. Also in the U.S., Epidiolex is sold to specialty pharmacies, wholesalers and specialty distributors. Sunosi is distributed through a retail channel consisting of numerous distributors who sell Sunosi to retail pharmacies. Defitelio is sold to hospital customers through subsidiary specialty distributors of McKesson Corporation, or McKesson. Zepzelca, Rylaze and Vyxeos are sold to customers through subsidiary specialty distributors of McKesson, AmerisourceBergen Corporation, or ABC, and Cardinal Health, Inc., or Cardinal. We have distribution services agreements made in the ordinary course of business with McKesson, ABC and Cardinal and a pharmacy services agreement with ESSDS that provides for the distribution of Xywav and Xyrem to patients. For more information regarding our relationship with ESSDS, see "Business—Our Commercialized Products—Xyrem" in this Part I, Item 1. Purchases are made on a purchase order basis.

In certain countries in Europe, Sunosi, Defitelio and Vyxeos are sold pursuant to marketing authorizations. We distribute these products through Durbin PLC, a U.K.-based wholesaler and distributor, and O&M Movianto Nederland BV, our centralized European logistics services provider, to hospitals and local wholesalers in Europe where we market these products

directly and, in other markets in Europe and elsewhere where we do not market these products directly, to local distributors and wholesalers. In certain countries in Europe, Epidyolex is sold pursuant to marketing authorizations. We distribute Epidyolex through a variety of wholesalers and distributors. Sativex is sold outside of the United States for the treatment of spasticity due to MS, pursuant to license agreements with commercial partners and directly to customers in the U.K. In countries where there is no marketing authorization, Defitelio, Vyxeos, Epidyolex and Sativex are sold pursuant to named patient programs, temporary use authorizations or similar authorizations.

We directly market Xyrem in Canada for the treatment of cataplexy in patients with narcolepsy. Xyrem is also sold in 21 countries by UCB (which has rights to market Xyrem in 54 countries).

Manufacturing

We have a manufacturing and development facility in Athlone, Ireland where we manufacture Xywav and Xyrem, a manufacturing and development facility in the U.K. in Kent Science Park, where we produce Epidiolex/Epidyolex and Sativex, and a manufacturing plant in Villa Guardia, Italy where we produce the defibrotide drug substance. We currently do not have our own commercial manufacturing or packaging capability for our other products, product candidates or their APIs. As a result, our ability to develop and supply products in a timely and competitive manner depends primarily on third party suppliers being able to meet our ongoing commercial and clinical trial needs for API, other raw materials, packaging materials and finished products. Our manufacturing facilities currently continue to be operational with essential staff onsite and office-based staff working onsite and remotely as business needs require.

Lead Marketed Products

Xywav. Xywav is manufactured at our Athlone facility. Xywav, like Xyrem, is a Schedule III controlled substance in the U.S. The API of Xywav are the calcium, magnesium, potassium and sodium salts of gamma-hydroxybutyric acid (as gamma-hydroxybutyric acid is the API for Xyrem), which are Schedule I controlled substances in the U.S. As a result, Xywav and Xyrem are subject to regulation by the U.S. Drug Enforcement Administration, or DEA, under the Federal Controlled Substances Act, or CSA, and its manufacturing and distribution are highly restricted. Quotas from the DEA are required in order to manufacture and package calcium, magnesium, potassium and sodium oxybate, Xywav and Xyrem in the U.S. For information related to DEA quota requirements, see “Business—Government Regulation—Other Post-Approval Pharmaceutical Product Regulation—Controlled Substance Regulations” in this Part I, Item 1.

Xyrem. Xyrem is manufactured by us in our Athlone facility and by Patheon Pharmaceuticals Inc., which we refer to together with its affiliates as Patheon, under a Master Manufacturing Services Agreement, or the Patheon Agreement, entered into with Patheon in 2015. We manufacture Xyrem in our Athlone facility for most of our U.S. commercial supply and rely on Patheon to supply Xyrem for other markets, though we are not required to purchase Xyrem exclusively from Patheon. The current term of the Patheon Agreement will expire in December 2024, subject to further automatic two-yearly extensions if Patheon is then providing manufacturing services for any product, unless either party provides prior notice of termination. In addition, we may terminate the Patheon Agreement for any reason upon 12 months’ prior written notice.

Siegfried USA, LLC and its European affiliates, or Siegfried, supply sodium oxybate, the API of Xyrem, to Patheon and our Athlone facility. Although Siegfried has been our only supplier of sodium oxybate since 2012, we have the right to purchase a portion of our worldwide requirements of sodium oxybate from other suppliers. The agreement with Siegfried expires in April 2024, subject to automatic three-year extensions until either party provides advance notice of its intent to terminate the agreement. During the term of the agreement and, under certain circumstances for 18 months after the agreement terminates, Siegfried is not permitted to manufacture sodium oxybate for any other company.

Epidiolex. Epidiolex/Epidyolex is manufactured by us in our Kent Science Park facility in the U.K. Epidiolex is a pharmaceutical formulation comprising highly purified plant-derived CBD. We cultivate our cannabinoid plants in the U.K. under highly controlled and standardized conditions.

Sunosi. Siegfried AG is our sole supplier of both the API and finished product for Sunosi for both commercial sale as well as development activities. Although Siegfried AG is currently our only manufacturer and supplier of Sunosi, we have the right to purchase a portion of our worldwide requirements of API and drug product from other suppliers. Under our agreement, we provide periodic rolling forecasts to Siegfried AG, and a portion of each rolling forecast is binding. The initial term of the agreement with Siegfried AG will expire in December 2024 and will then be subject to automatic one-year extensions until either party provides advance notice of its intent to terminate the agreement. Solriamfetol, the API of Sunosi, and Sunosi were designated Schedule IV controlled substances by the DEA under the CSA.

Sativex. Sativex is manufactured by us in our Kent Science Park facility in the U.K. Sativex (nabiximols) is a complex botanical mixture formulated from extracts of the cannabis sativa plant that contains the principal cannabinoids THC and CBD as well as specific minor cannabinoids and other non-cannabinoid components. We cultivate our cannabinoid plants in the U.K. under highly controlled and standardized conditions.

Zepzelca. Zepzelca is manufactured by Baxter. The initial term of the agreement with Baxter will expire in December 2023 and will then be subject to automatic two-year extensions, unless either party provides advance notice of its intent to terminate the agreement. PharmaMar retains manufacturing rights for the API for U.S. and Canadian commercial supply of Zepzelca. We also entered into a manufacturing agreement for ongoing commercial supply of the drug product Zepzelca with GP Pharm S.A.

Rylaze. Rylaze is currently manufactured by Patheon, and the API of Rylaze is manufactured by AGC Biologics A/S. The initial term of the agreement with Patheon will expire in December 2025 and will then be subject to automatic two-year extensions, unless either party provides advance notice of its intent to terminate the agreement. The initial term of the agreement with AGC Biologics A/S will expire in October 2026 and will then be subject to automatic three-year extensions, unless either party provides advance notice of its intent to terminate the agreement.

Vyxeos. Vyxeos is manufactured by Baxter Oncology GmbH, or Baxter, which is a sole source supplier from a single site location, using our CombiPlex technology platform. CombiPlex products represent formulations with increased manufacturing complexities associated with producing drug delivery vehicles encapsulating two or more drugs that are maintained at a fixed ratio and, in the case of Vyxeos, two drugs that are co-encapsulated in a freeze-dried liposomal format. Our manufacturing agreement with Baxter expires in August 2025, subject to automatic three-year renewal terms, unless either party provides advance notice of its intent to terminate the agreement. While other contract manufacturers may be able to produce Vyxeos, the proprietary technology that supports the manufacture of Vyxeos is not easily transferable. The marketing authorization in the EU for Vyxeos also requires us to comply with certain manufacturing-related post-approval commitments.

Defitelio. We are our own sole supplier of, and we believe that we are currently the sole worldwide producer of, the defibrotide API. We manufacture the defibrotide API from porcine DNA in a single facility located in Villa Guardia, Italy. Patheon currently processes the defibrotide API into its finished vial form under a specific product agreement entered into under a separate agreement with Patheon. Patheon is the sole provider of our commercial and clinical supply of Defitelio; however, we are not required to purchase Defitelio exclusively from Patheon. If Patheon does not or is not able to supply us with Defitelio for any reason, it may take time and resources to implement and execute the necessary technology transfer to another processor, and such delay could negatively impact our anticipated revenues from Defitelio and could potentially cause us to breach contractual obligations with customers or to violate local laws requiring us to deliver the product to those in need.

Product Candidates

For discussion of the challenges we face with respect to supply of our products and product candidates, see the risk factor under the heading *"Delays or problems in the supply of our products for sale or for use in clinical trials, loss of our single source suppliers or failure to comply with manufacturing regulations could materially and adversely affect our business, financial condition, results of operations and growth prospects"* in Part I, Item 1A of this Annual Report on Form 10-K.

Patents and Proprietary Rights

We actively seek to patent, or to acquire or obtain licenses to third party patents, to protect our products and product candidates and related inventions and improvements that we consider important to our business. We own a portfolio of U.S. and non-U.S. patents and patent applications and have licensed rights to a number of issued patents and patent applications. Our owned and licensed patents and patent applications cover or relate to our products and product candidates, including certain formulations, used to treat particular conditions, distribution methods and methods of administration, drug delivery technologies and delivery profiles and methods of making and use. Patents extend for varying periods according to the date of the patent filing or grant and the legal term of patents in the various countries where patent protection is obtained. The patent laws of non-U.S. countries differ from those in U.S., and the degree of protection afforded by non-U.S. patents may be different from the protection offered by U.S. patents. In addition to patents, our products and product candidates are in some instances protected by various regulatory exclusivities. For a description of those exclusivities and their regulatory background, see "Business—Government Regulation—Marketing Exclusivity—The Hatch-Waxman Act" in this Part I, Item 1.

The patents, patent applications and regulatory exclusivities that relate to our marketed products include:

- *Xywav.* We have 12 U.S. patents that relate to Xywav. These patents expire from 2023 to 2033. In addition, we have patent applications that relate to Xywav for use in additional indications that would, if issued, expire between 2040 and 2041. Xywav has been granted ODE by FDA to treat narcolepsy through 2027 and to treat IH through 2028.
- *Xyrem.* We currently have six issued, unexpired patents in the U.S. relating to Xyrem. These patents are listed in FDA's publication "Approved Drug Products with Therapeutic Equivalence Evaluations," or the Orange Book. Our patents relate to Xyrem's restricted distribution system and a drug-drug interaction, or DDI, between Xyrem and divalproex sodium. In October 2018, as a result of FDA's grant of pediatric exclusivity, an additional six months was added to the original expiration dates of all of our Orange Book-listed patents that existed at that time. As a result,

our Orange Book-listed patents have periods of exclusivity between December 2022 and September 2033. Some of our Xyrem patents have been subject to patent litigation with the companies who filed ANDAs seeking to market a generic version of Xyrem, including challenge through the inter partes review, or IPR, procedures of the Patent Trial and Appeal Board, or PTAB, of the U.S. Patent and Trademark Office, or USPTO. Some IPR petitions were dismissed by the PTAB. However, in July 2018, the United States Court of Appeals for the Federal Circuit upheld on appeal PTAB decisions finding that six patents associated with the Xywav and Xyrem REMS and three claims of a seventh REMS patent were unpatentable. As a result, we will not be able to enforce patents or claims that the PTAB found unpatentable. Although we have settled all patent litigation against the nine companies that filed ANDAs, it is possible that additional companies may challenge our U.S. patents for Xyrem in the future. For a description of our Xyrem settlements, see the risk factor under the heading "*The introduction of new products in the U.S. market that compete with, or otherwise disrupt the market for, our oxybate products and product candidates would adversely affect sales of our oxybate products and product candidates*" in Part I, Item 1A of this Annual Report on Form 10-K.

A Xyrem formulation patent that had issued in multiple non-U.S. countries expired in 2019. The European Patent Office has issued a method of administration patent relating to the DDI between Xyrem and divalproex sodium that will expire in 2034. That patent is licensed to UCB as the marketing authorization holder outside of the U.S. and Canada, and UCB has the right to enforce it. In addition to our issued patents, we have patent applications relating to Xyrem pending in the U.S. and other countries.

- *Epidiolex.* Our patent portfolio relating to the use of CBD in the treatment of epileptic encephalopathies includes 90 distinct patent families that are either granted or filed. Most of the patent families in this portfolio claim the use of CBD in the treatment of particular childhood epilepsy syndromes, seizure sub-types and interactions with other concomitantly dosed anti-seizure drugs. To date, we have obtained 21 issued U.S. patents, including patents with claims for the use of CBD for the treatment of convulsive, drop and atonic seizures associated with both LGS and DS, an oral composition of CBD, as well as the use of CBD with clobazam, and the teaching that dose adjustment may be needed when concomitantly prescribed. These issued patents are directly aligned with the Epidiolex label, and we have listed them in the Orange Book. These patents have expiry between 2022 and 2041. We have filed corresponding patent applications in many jurisdictions worldwide, including Europe, UK, Canada, Japan, Mexico, Australia and New Zealand. The USPTO has granted a patent based on data that demonstrates that Epidiolex provides a benefit over synthetic CBD in an animal model of epilepsy, which has an expiry date of 2039 and we have listed it in the Orange Book. Epidiolex has received ODE to treat seizures associated with LGS and DS through 2025 and TSC through 2027.
- *Sunosi*. We acquired worldwide development, manufacturing and commercial rights to solriamfetol from Aerial BioPharma LLC, or Aerial, in 2014, including Aerial's patent rights relating to solriamfetol, other than in certain jurisdictions in Asia where SK Biopharmaceuticals Co., Ltd. retains rights. We have a portfolio of U.S. and non-U.S. patents and patent applications for solriamfetol relating to various compositions, formulations and methods of use. Four of our U.S. patents are method of use patents covering treatment of sleep-related conditions expiring between 2026 and 2027 and another U.S. patent is directed to dose escalation regimens expiring in 2038. Two other U.S. patents cover, respectively, the formulation of solriamfetol and the method of treating select conditions with formulations of solriamfetol (both expiring in 2037). A request for a patent term extension for one of the above method of use patents has been filed. Requests for Supplementary Protection Certificate in certain European validation countries for a related European patent have been granted in Austria, Denmark, France, Ireland, Italy, Netherlands, Spain and Sweden (expiring in 2031) and remain pending in the others. Sunosi has also been granted ODE for narcolepsy and new chemical entity exclusivity in the U.S.
- *Sativex.* In the U.S., our patents (and our pending applications if they issue) relating to nabiximols would expire on various dates between 2022 and 2029, excluding possible patent term extensions. We have at least seven different patent families containing one or more pending and/or issued patents directed to the nabiximols formulation, the medical use of nabiximols, the extracts from which nabiximols is composed, the extraction technique used to produce the extracts and the therapeutic use of nabiximols. Due to the product's significant complexity, we believe that nabiximols will benefit from strong long-term market regulatory protection.
- *Zepzelca*. In December 2019, we entered into an exclusive license agreement with PharmaMar pursuant to which we obtained exclusive U.S. development and commercialization rights to Zepzelca. In October 2020, we entered into the amended license agreement which expanded our exclusive license to include rights to develop and commercialize Zepzelca in Canada. We have a portfolio of in-licensed U.S. and Canadian patents for lurbinectedin relating to compositions, methods of use, and processes. For example, one U.S. patent (expiring in 2024) covers a genus of compounds, including lurbinectedin, and use in treating various cancers. A request for a patent term extension for this U.S. patent has been filed and, if granted, would extend to 2029. A request for extension (CSP) has also been filed in Canada. Zepzelca has also been granted orphan drug exclusivity for the treatment of adults with metastatic

SCLC with disease progression on or after platinum-based chemotherapy until 2027 and new chemical entity exclusivity until 2025 in the U.S.

- *Rylaze*. In 2016, we obtained worldwide rights from Pfenex, Inc., including Pfenex's patent rights relating to Rylaze, to develop and commercialize multiple early-stage hematology product candidates, including a license to two U.S. process patents relating to Rylaze, with respective expirations in 2026 and 2038. Pfenex has been acquired by Ligand Pharmaceuticals Incorporated. Rylaze has been granted ODE for the treatment of patients with ALL or LBL until 2028. We have two patent application families relating to dosing regimens. One covers the current dosing regimen (25mg/m2 intramuscularly every 48 hours), while the other covers various dosing regimens of interest. If issued, these would expire in 2040 and 2042, respectively. Another application relating to formulations of asparaginase would expire in 2042 if issued.
- *Vyxeos.* We have a portfolio of U.S. and non-U.S. patents and patent applications for Vyxeos and the CombiPlex technology platform relating to various compositions and methods of making and use. These include seven U.S. patents covering Vyxeos compositions and methods of use expiring between 2025 and 2034 and two U.S. patents covering CombiPlex (which also cover Vyxeos) expiring in January 2027. These patents are listed in the Orange Book. Vyxeos has been granted ODE by FDA until August 2024, seven years from its FDA approval, for the treatment of adults with newly-diagnosed t-AML or AML-MRC. In March 2021, FDA approved an expanded label for Vyxeos for the treatment of t-AML or AML-MRC in pediatric patients 1 year and older. In addition, Vyxeos has been granted orphan drug designation by the EC until August 2028, ten years from its EC approval for the treatment of adults with newly-diagnosed t-AML or AML-MRC and was approved by Health Canada for treatment of adults with newly diagnosed t-AML or AML-MRC in April 2021.
- *Defitelio*. The unique process of deriving defibrotide from porcine DNA is extensive and uses both chemical and biological processes that rely on complex characterization methods. We have U.S. and non-U.S. patents and patent applications relating to various compositions, methods of use and methods of characterization, with the issued patents expiring at various times between 2021 and 2035. One U.S. patent is listed in the Orange Book and an additional allowed patent is expected to be Orange Book listed in 2022. Defibrotide has been granted ODE by FDA to treat and prevent VOD until March 2023. Defibrotide has also been granted orphan drug designation by the EC and the Korean Ministry of Food and Drug Safety to treat and prevent VOD, by the Commonwealth of Australia-Department of Health for the treatment of VOD and by the EC for the prevention of acute Graft-versus-Host Disease, or aGvHD, and have also received approvals in Canada, Brazil and Switzerland. We acquired the rights to defibrotide for the treatment and prevention of VOD in North America, Central America and South America from Sigma-Tau Pharmaceuticals, Inc. in 2014.

The patents and/or patent applications that relate to our product candidates include:

- *Suvecaltamide (JZP385).* Through the acquisition of Cavion in 2019, we obtained a portfolio of U.S. and non-U.S. patents and patent applications, including rights relating to compositions and methods of using suvecaltamide. The portfolio includes a U.S. composition of matter patent relating to suvecaltamide, which expires in 2027, but which can be extended to 2032 depending on regulatory approval. Two further U.S. patents to the treatment of specific conditions (Angelman Syndrome and memory and cognitive disorders) provide supplemental protection to 2038.
- *JZP150.* Through the asset purchase and exclusive license agreement with SpringWorks in 2020, we obtained a license to a portfolio of U.S. and non-U.S. patents and patent applications, including rights relating to compositions and methods of using JZP150. The portfolio includes a U.S. composition of matter patent relating to JZP150, which expires in 2029.

In addition, we have rights to a number of trademarks and service marks, and pending trademark and service mark applications, in the U.S. and elsewhere in the world to further protect the proprietary position of our products. For a discussion of the challenges we face in obtaining or maintaining patent and/or trade secret protection, see the risk factors under the heading "Risks Related to Our Intellectual Property" in Part I, Item 1A of this Annual Report on Form 10-K.

Government Regulation

As a global pharmaceutical company, our activities are subject to extensive regulation in the U.S., Europe and other countries where we do business. Regulatory requirements encompass the entire life cycle of pharmaceutical products, from research and development activities to marketing approval, manufacturing, labeling, packaging, adverse event and safety reporting, storage, advertising, promotion, sale, pricing and reimbursement, recordkeeping, distribution, importing and exporting. Regulations differ from country to country and are constantly evolving.

Testing and Approval of Pharmaceutical Products

We are not permitted to market a product in a country until we receive approval from the relevant regulatory authority, such as FDA in the U.S. and the EC or the competent authorities of the EU member states. An application for marketing approval must contain information generated by the applicant, also called a sponsor, demonstrating the quality, safety and efficacy of the product candidate, including data from preclinical and clinical trials, proposed product packaging and labeling and information pertaining to product formulation and the manufacture and analytical testing of the API and the finished product.

In the U.S., FDA reviews and, if warranted, approves applications for marketing approval. The process for obtaining marketing approval in the U.S. for a drug or biologic product candidate generally includes:

- conducting preclinical laboratory and animal testing and submitting the results to FDA in an investigational new drug, or IND, application requesting approval to test the product candidate in human clinical trials;
- conducting adequate and well-controlled human clinical trials to establish the safety and efficacy of the product candidate in the desired indication;
- submitting an NDA, sNDA, or BLA, as appropriate, to FDA seeking approval for a specific indication; and
- completing inspections by FDA of the facilities where the product candidate is manufactured, analyzed and stored to demonstrate compliance with current Good Manufacturing Practices, or cGMP, and any requested FDA audits of the clinical trial sites that generated the data supporting the application.

Human clinical trials conducted before approval of a product generally proceed in three sequential phases, although the phases may overlap. In Phase 1, the initial introduction of the product candidate in humans, the product candidate is typically tested to assess metabolism, pharmacokinetics, pharmacological actions and tolerability, including side effects associated with increasing doses. Phase 2 usually involves clinical trials in a limited patient population to determine the effectiveness of the product candidate for a particular indication or indications, dosage tolerance and optimum dosage and to identify common adverse effects and safety risks. If a product candidate demonstrates evidence of effectiveness and an acceptable safety profile in Phase 2, Phase 3 clinical trials are undertaken to obtain additional information about clinical efficacy and safety in a larger number of patients. Clinical trials must be conducted in accordance with specific protocols, as well as FDA requirements related to conducting the trials and recording and reporting the results, commonly referred to as good clinical practices, to ensure that the resulting data are credible and accurate and that the trial participants are adequately protected. FDA enforces good clinical practices through periodic inspections of trial sponsors, clinical investigators and trial sites.

Once an NDA, sNDA or BLA has been compiled and submitted, FDA performs an initial review before it accepts the application for filing. FDA may refuse to file an application and/or request additional information before acceptance. Once accepted for filing, FDA begins an in-depth review of the application. Under the current goals and policies agreed to by FDA under the PDUFA for a new molecular entity, FDA has ten months from the filing decision in which to complete its initial review of a standard application and respond to the applicant, and six months from the filing decision for a priority application. FDA does not always meet its PDUFA goal dates, and in certain circumstances, the PDUFA goal date may be extended.

FDA also has various programs, including Fast Track, Priority Review, Breakthrough Therapy and Accelerated Approval (Subpart H and E), RTOR pilot program, that are intended to expedite the process for reviewing certain applications and/or provide for approval on the basis of surrogate endpoints or restricted distribution. Generally, products may be eligible for one or more of these programs if they are intended for serious or life-threatening diseases or conditions, have potential to address unmet medical needs, or may provide meaningful benefit over existing treatments. For example, FDA granted Vyxeos Breakthrough Therapy and Fast Track designations and granted Priority Review with respect to our NDA for Vyxeos for the treatment of t-AML and AML-MRC that was approved in August 2017. In addition, a priority review voucher, or PRV, may be used to obtain priority review by FDA for one of our future regulatory submissions. We used the PRV we acquired in May 2018 to obtain priority review for our Xywav for the treatment of IH sNDA, which was approved by FDA in August 2021. In June 2020, FDA granted Accelerated Approval to Zepzelca for relapsed SCLC. In December 2020, we initiated the submission of a BLA for Rylaze for ALL under the RTOR pilot program, which was approved by FDA in June 2021.

During its review of an application, FDA evaluates whether the product demonstrates the required level of safety and efficacy for the indication for which approval is sought and conducts the inspections and audits described above. FDA may also refer an application to an advisory committee, typically a panel of clinicians, for review, evaluation and a non-binding recommendation as to whether the application should be approved. When FDA completes its evaluation, it issues either an approval letter or a complete response letter. A complete response letter generally outlines what FDA considers to be the deficiencies in the application and may indicate that substantial additional testing or information is required prior to FDA approval of the product. If and when identified deficiencies have been addressed to FDA's satisfaction after a review of the resubmission of the application FDA will issue an approval letter.

Even if a product is approved, the approval may be subject to limitations based on FDA's interpretation of the data submitted in the application. For example, as a condition of approval, FDA may require the sponsor to agree to certain post-marketing requirements, such as conducting Phase 4, or post-approval, clinical trials to gain additional safety data or to document a clinical benefit in the case of products approved under Accelerated Approval regulations. FDA's approval of the NDA for Defitelio included a number of post-marketing commitments and requirements, including the requirement that we conduct a clinical trial to analyze the safety of defibrotide versus best supportive care in the prevention of VOD in adult and pediatric patients. For its approval of Vyxeos, FDA required that we conduct a safety study to characterize infusion-related reactions in patients treated with Vyxeos and a clinical trial to determine dosing to minimize toxicity in patients with moderate and severe renal impairment. Further, FDA granted Accelerated Approval to Zepzelca for relapsed SCLC based on data from a Phase 2 trial, which approval is contingent upon verification and description of clinical benefit in a post-marketing clinical trial.

In addition, if FDA determines that a REMS is necessary to ensure that the benefits of the product outweigh the risks, a sponsor may be required to include a proposed REMS (either as part of the application or after approval), which may include a patient package insert or a medication guide to provide information to consumers about the product's risks and benefits; a plan for communication to healthcare providers; or conditions on the product's prescribing or distribution referred to as elements to assure safe use. Xywav and Xyrem are required to have a REMS. For more discussion regarding the Xywav and Xyrem REMS, see the risk factors under the headings "*The distribution and sale of our oxybate products are subject to significant regulatory restrictions, including the requirements of a REMS, and these regulatory requirements subject us to risks and uncertainties, any of which could negatively impact sales of Xywav and Xyrem*" and "Risks Related to Our Intellectual Property" in Part I, Item 1A of this Annual Report on Form 10-K.

The EU and many individual countries have regulatory structures similar to the U.S. for conducting preclinical and clinical testing and applying for marketing approval or authorization, although specifics may vary widely from country to country. Clinical trials in the EU must be conducted in accordance with the requirements of the EU Clinical Trials Regulation and applicable good clinical practice standards. In the EU, there are several procedures for requesting marketing authorization which can be more efficient than applying for authorization on a country-by-country basis. There is a "centralized" procedure allowing submission of a single marketing authorization application to the European Medicines Agency, or EMA. If the EMA issues a positive opinion, the EC will grant a centralized marketing authorization that is valid in all EU member states and three of the four European Free Trade Association countries (Iceland, Liechtenstein and Norway). The centralized procedure is mandatory for certain medicinal products, including orphan medicinal products and biotechnology-derived medicinal products, and optional for others. There is also a "decentralized" procedure allowing companies to file identical applications to several EU member states simultaneously for product candidates that have not yet been authorized in any EU member state and a "mutual recognition" procedure allowing companies that have a product already authorized in one EU member state to apply for that authorization to be recognized by the competent authorities in other EU member states. The U.K.'s withdrawal from the EU on January 31, 2020, commonly referred to as Brexit, has created uncertainty concerning the future relationship between the U.K. and the EU. Among the changes that have had a direct impact are that Great Britain (England, Scotland and Wales) is now treated as a third country. To mitigate the immediate impact of this in December 2020, the EU and U.K. reached an agreement in principle on the framework for their future relationship, the EU-U.K. Trade and Cooperation Agreement, or TCA. With regard to EU regulations, Northern Ireland continues to follow the EU regulatory rules. As part of the TCA, the EU and the U.K. recognize Good Manufacturing Practice, or GMP, inspections carried out by the other party and the acceptance of official GMP documents issued by the other party. The TCA also encourages, although it does not oblige, the parties to consult one another on proposals to introduce significant changes to technical regulations or inspection procedures. Among the areas of absence of mutual recognition are batch testing and batch release. The U.K. has unilaterally agreed to accept EU batch testing and batch release for a period of at least 2 years until January 1, 2023. However, the EU continues to apply EU laws that require batch testing and batch release to take place in the EU territory. This means that medicinal products that are tested and released in the U.K. must be retested and re-released when entering the EU market for commercial use. As regards marketing authorizations, Great Britain has introduced a separate regulatory submission process, approval process and a separate national marketing authorization. Northern Ireland, however, continues to be covered by the marketing authorizations granted by the EC.

The maximum timeframe for the evaluation of an application in the EU under the centralized procedure is 210 days, subject to certain exceptions and clock stops. An initial marketing authorization granted in the EU is valid for five years, with renewal subject to re-evaluation of the risk-benefit profile of the product. Once renewed, the authorization is usually valid for an unlimited period unless the national competent authority or the EC decides on justified grounds to proceed with one additional five-year renewal.

In the EU, if an applicant can demonstrate that comprehensive data on the efficacy and safety of the product under normal conditions of use cannot be provided due to certain specified objective and verifiable reasons, products may be granted marketing authorization "under exceptional circumstances." A marketing authorization granted under exceptional circumstances is valid for five years, subject to an annual reassessment of conditions imposed by the EC. The marketing authorization in the EU for Defitelio was granted under exceptional circumstances because it was not possible to obtain

complete information about the product due to the rarity of the disease and because ethical considerations prevented conducting a study directly comparing Defitelio with best supportive care or a placebo. As a result, the marketing authorization requires us to comply with a number of post-marketing obligations, including obligations relating to the manufacture of the drug substance and finished product, the submission of data concerning patients treated with the product collected through a third-party patient registry and the establishment of a multi-center, multinational and prospective observational patient registry to investigate the long-term safety, health outcomes and patterns of utilization of Defitelio during normal use. We are in the process of conducting the post-authorization study in the EU to provide further data on long-term safety, health outcomes and patterns of utilization of Defitelio in normal use.

Similar to the use of REMS in the U.S. to ensure that the benefits of a product outweigh its risks, in the EU and other countries we are required and may, in the future in relation to new products, be required to agree to post-marketing obligations or conditions in the marketing authorization for our products, to include a patient package insert or a medication guide to provide information to consumers about the product's risks and benefits, to implement a plan for communication to healthcare providers, and to impose restrictions on the product's distribution. For example, the marketing authorization in the EU for Vyxeos requires us to comply with certain manufacturing-related post-approval commitments.

After approval, certain changes to the approved product, such as adding new indications, making certain manufacturing changes, modifying a REMS, or making certain additional labeling claims, are subject to further regulatory review and approval. Obtaining approval for a new indication generally requires that additional clinical studies be conducted to demonstrate that the product is safe and effective for the new intended use. Such regulatory reviews can result in denial or modification of the planned changes, or requirements to conduct additional tests or evaluations that can substantially delay or increase the cost of the planned changes.

Manufacture of Pharmaceutical Products

The manufacturing process for pharmaceutical products is highly regulated, and regulators may shut down manufacturing facilities that they believe do not comply with regulations. We and the third party suppliers of our products are subject to cGMP, which are extensive regulations governing manufacturing processes, stability testing, recordkeeping and quality standards as defined by FDA, the EC, the EMA, competent authorities of EU member states and other regulatory authorities. FDA also periodically inspects manufacturing facilities and the sponsor's and manufacturer's records related to manufacturing, and assesses compliance with cGMP. Following such inspections, FDA may issue notices on Form FDA 483 and warning letters. In addition to Form FDA 483 notices and warning letters, failure to comply with the statutory and regulatory requirements may result in suspension of manufacturing, product seizure, withdrawal of the product from the market, administrative, civil and criminal penalties, among other enforcement remedies both in the U.S. and in non-U.S. countries.

In the EU, a manufacturing authorization is required to manufacture medicinal products, and the manufacturing authorization holder must comply with various requirements set out in applicable EU laws, regulations and guidance. These requirements include compliance with EU cGMP standards when manufacturing products and their APIs, including APIs manufactured outside of the EU with the intention of importing them into the EU. In addition to inspection reports, manufacturers and marketing authorization holders may be subject to civil, criminal or administrative sanctions, including suspension of manufacturing authorization, in cases of non-compliance with the EU or EU member states' requirements applicable to manufacturing.

Sales and Marketing of Pharmaceutical Products

Advertising and Promotional Activities

FDA regulates advertising and promotional activities for products in the U.S., requiring advertising, promotional materials and labeling to be truthful and not misleading, and products to be marketed only for their approved indications and in accordance with the provisions of the approved label. FDA actively investigates allegations of off-label promotion in order to enforce regulations prohibiting these types of activities. FDA routinely issues informal and more formal communications such as untitled letters or warning letters interpreting its authority over these matters. While such communications may not be considered final agency decisions, many companies may decide not to contest the agency's interpretations so as to avoid disputes with FDA, even if they believe the claims they were making to be truthful, not misleading and otherwise lawful.

In the EU, the advertising and promotion of our products are subject to laws governing promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. For example, applicable laws require that promotional materials and advertising in relation to medicinal products comply with the product's Summary of Product Characteristics, or SmPC, as approved by the competent authorities in connection with a marketing authorization approval. The SmPC is the document that provides information to physicians concerning the safe and effective use of the product. Promotional activity that does not comply with the SmPC is considered off-label and is prohibited in the EU. Other applicable laws at the EU level and in the individual EU member states also apply to the advertising and promotion of medicinal products, including laws that prohibit the direct-to-consumer advertising of prescription-only medicinal products and

further limit or restrict the advertising and promotion of our products to the general public and to health care professionals. Violations of the rules governing the promotion of medicinal products in the EU could be penalized by administrative measures, fines and imprisonment.

Fraud and Abuse

We are also subject to numerous fraud and abuse laws and regulations globally. In the U.S., there are a variety of federal and state laws restricting certain marketing practices in the pharmaceutical industry pertaining to healthcare fraud and abuse, including anti-kickback laws and false claims laws. Our sales, marketing, patient support and medical activities may be subject to scrutiny under these laws. The U.S. federal healthcare program Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving anything of value to induce (or in return for) the referral of business, including the purchase, recommendation or prescription of a particular drug reimbursable under Medicare, Medicaid or other federally financed healthcare programs. The statute has been interpreted to apply to arrangements between pharmaceutical companies on one hand and patients, prescribers, purchasers and formulary managers on the other. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain common manufacturer business arrangements and activities from prosecution and administrative sanction, the exemptions and safe harbors are drawn narrowly and are subject to regulatory revision or changes in interpretation by the U.S Department of Justice, or DOJ, and the Office of Inspector General of the U.S. Department of Health and Human Services, or OIG. Practices or arrangements that involve remuneration may be subject to scrutiny if they do not qualify for an exemption or safe harbor. For example, in November 2020, the OIG issued a Special Fraud Alert to highlight certain inherent risks of remuneration related to speaker programs sponsored by drug and device companies, which do not fall under either safe harbor or statutory exception protection. The Special Fraud Alert sent a clear signal that speaker programs will be subject to potentially heightened enforcement scrutiny, in particular for those programs with certain characteristics identified as risk factors by OIG, including meals exceeding modest value or where alcohol is made available; lack of substantive or new content presented; programs held at venues not conducive to the exchange of educational information; repeat attendees or attendees without a legitimate business interest; sales or marketing influence on speaker selection; and excessive speaker compensation. Violations of the federal Anti-Kickback Statute may be established without providing specific intent to violate the statute, and may be punishable by civil, criminal, and administrative fines and penalties, damages, imprisonment, and/or exclusion from participation in federal healthcare programs.

The federal civil False Claims Act prohibits, among other things, any person from knowingly presenting, or causing to be presented, a false or fraudulent claim for payment of federal funds, or knowingly making, or causing to be made, a false statement to get a false claim paid. A claim resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim. The False Claims Act also permits a private individual acting as a “whistleblower” to bring actions on behalf of themselves and the federal government alleging violations of the statute and to share in any monetary recovery. Violations of the False Claims Act may result in significant financial penalties (including mandatory penalties on a per claim or statement basis), treble damages and exclusion from participation in federal health care programs.

Pharmaceutical companies are subject to other federal false claim and statements laws, some of which extend to non-government health benefit programs. For example, the healthcare fraud provisions under the Health Insurance Portability and Accountability Act of 1996 and its implementing regulations, or HIPAA, impose criminal liability for, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any health care benefit program, including private third party payors, or falsifying or covering up a material fact or making any materially false or fraudulent statement in connection with the delivery of or payment for health care benefits, items or services. Violations of HIPAA fraud provisions may result in criminal, civil and administrative penalties, fines and damages, including exclusion from participation in federal healthcare programs.

The majority of individual states also have statutes or regulations similar to the federal anti-kickback law and the False Claims Act, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor. Other states restrict whether and when pharmaceutical companies may provide meals to health care professionals or engage in other marketing-related activities, and certain states and cities require identification or licensing of sales representatives.

Other Post-Approval Pharmaceutical Product Regulation

Safety Reporting/Pharmacovigilance

FDA, the EMA and other governmental authorities track information on side effects and adverse events reported during clinical studies and after marketing approval. We are required to file periodic safety update reports with the authorities concerning adverse events. If, upon review, an authority determines that any events and/or reports indicate a trend or signal, they can require a change in a product label, restrict sales and marketing, require post-approval safety studies, require a labor intensive collection of data regarding the risks and benefits of marketed products and ongoing assessments of those risks and benefits and/or require or conduct other actions, potentially including withdrawal or suspension of the product from the market. For example, if the EMA has concerns that the risk-benefit profile of a product has changed, it can, following an investigation

procedure, adopt an opinion advising that the existing marketing authorization for the product be varied or suspended and requiring the marketing authorization holder to conduct post-authorization safety studies. The opinion is then submitted for approval by the EC. Also, from time to time, FDA issues drug safety communications on its adverse event reporting system based on its review of reported adverse events.

FDA and the competent authorities of the EU member states on behalf of the EMA also periodically inspect our records related to safety reporting. Following such inspections, FDA may issue notices on FDA Form 483 and warning letters that could cause us to modify certain activities. An FDA Form 483 notice, if issued, can list conditions FDA investigators believe may have violated relevant FDA regulations or guidance. Failure to adequately and promptly correct the observation(s) can result in a warning letter or other regulatory enforcement action. Similarly, the EMA's Pharmacovigilance Risk Assessment Committee may propose to the Committee for Medicinal Products for Human Use that the marketing authorization holder be required to take specific steps. Non-compliance can lead to the variation, suspension or withdrawal of marketing authorization or imposition of financial penalties or other enforcement measures.

Sunshine Act and Transparency Laws

The Physician Payment Sunshine Act requires tracking of payments and transfers of value to physicians and teaching hospitals and ownership interests held by physicians and their families, and reporting to the federal government and public disclosure of these data. Beginning in 2022, reporting will also be required of information regarding payments and transfers of value provided to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, and certified nurse-midwives. A number of states now require pharmaceutical companies to report expenses relating to the marketing and promotion of pharmaceutical products and to report gifts and payments to healthcare providers in the states. Government agencies and private entities may inquire about our marketing practices or pursue other enforcement activities based on the disclosures in those public reports.

Outside the U.S., interactions between pharmaceutical companies and physicians are also governed by strict laws, regulations, industry self-regulation codes of conduct and physicians' codes of professional conduct. The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products, which is prohibited in the EU, is governed by the national anti-bribery laws of the EU member states, as described below in "Business—Government Regulation—Anti-Corruption Legislation" in this Part I, Item 1. Violation of these laws could result in substantial fines and imprisonment. Certain EU member states, or industry codes of conduct, require that payments made to physicians be publicly disclosed. Moreover, agreements with physicians must often be the subject of prior notification and approval by the physician's employer, his/her competent professional organization, and/or the competent authorities of the individual EU member states. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

Controlled Substance Regulations

A drug product approved by FDA may be subject to scheduling as a controlled substance under the CSA depending on the drug's potential for abuse. Controlled substances that are pharmaceutical products are subject to a high degree of regulation under the CSA, which establishes, among other things, certain registration, manufacturing quotas, security, recordkeeping, reporting, import, export and other requirements administered by the DEA. The DEA classifies controlled substances into five schedules. Schedule I substances by definition have a high potential for abuse, have no currently "accepted medical use" in the U.S., lack accepted safety for use under medical supervision, and may not be prescribed, marketed or sold in the U.S. Pharmaceutical products approved for use in the U.S. may be listed as Schedule II, III, IV or V, with Schedule II substances considered to present the highest potential for abuse or dependence and Schedule V substances the lowest relative risk of abuse. The API of Xywav and Xyrem, oxybate salts, are regulated by the DEA as Schedule I controlled substances, and Xywav and Xyrem are regulated as Schedule III controlled substances. The API of Sunosi, solriamfetol, and Sunosi are regulated as Schedule IV controlled substances. Individual countries also impose similar requirements for controlled substances. Nabiximols and certain other product candidates we are developing contain controlled substances as defined in the CSA. Drug products approved by FDA that contain cannabis or cannabis extracts may be controlled substances and will be rescheduled to Schedules II-V after approval, or, like Epidiolex, removed completely from the schedules by operation of other laws.

The DEA limits the quantity of certain Schedule I controlled substances that may be manufactured and procured in the U.S. in any given calendar year through a quota system and, as a result, quotas from the DEA are required in order to manufacture and package sodium oxybate and Xyrem in the U.S. Accordingly, we require DEA quotas for Siegfried, our U.S. based sodium oxybate supplier, to procure sodium oxybate and for Patheon, our U.S.-based Xyrem supplier, to obtain the sodium oxybate from Siegfried in order to manufacture and supply us with Xyrem. Xywav and Xyrem manufactured at our plant in Ireland enters the U.S. as a Schedule III drug and thus does not require a manufacturing quota.

As Schedule III drugs, Xywav and Xyrem are also subject to DEA import volume limits and state regulations relating to manufacturing, storage, distribution and physician prescription procedures, including limitations on prescription refills. In addition, the third parties who perform our clinical and commercial manufacturing, distribution, dispensing and clinical studies

for Xywav and Xyrem are required to maintain necessary DEA registrations and state licenses. The DEA periodically inspects facilities for compliance with its rules and regulations.

Other Regulations

There are many other requirements and restrictions in the U.S. and elsewhere imposed on pharmaceutical companies and their activities, including those related to the posting of information relating to clinical studies and their outcomes, the export and importation of products, required authorizations for distributors, the identification or licensing of sales representatives, restrictions on the ability of manufacturers to offer co-pay support to patients for certain prescription drugs, implementation of required compliance programs or marketing codes of conduct, protection of the environment, taxation and work safety. Non-compliance with such requirements may result in civil, criminal or administrative sanctions.

Anti-Corruption Legislation

Our business activities outside of the U.S. are subject to the U.S. Foreign Corrupt Practices Act, or FCPA, and similar anti-bribery or anti-corruption laws, regulations, industry self-regulation codes of conduct and physicians' codes of professional conduct or rules of other countries in which we operate, including the U.K. Bribery Act of 2010, or the U.K. Bribery Act. The FCPA and similar anti-corruption laws in other countries generally prohibit the offering, promising, giving, or authorizing others to give anything of value, either directly or indirectly, to U.S. or non-U.S. government officials in order to improperly influence any act or decision, secure an improper advantage, or obtain or retain business. The FCPA also requires public companies to make and keep books and records that accurately and fairly reflect the transactions of the company and to devise and maintain an adequate system of internal accounting controls. The U.K. Bribery Act prohibits giving, offering, or promising bribes to any person, including U.K. and non-U.K. government officials and private persons, as well as requesting, agreeing to receive, or accepting bribes from any person. In addition, under the U.K. Bribery Act, companies that carry on a business or part of a business in the U.K. may be held liable for bribes given, offered or promised to any person, including U.K. and non-U.K. government officials and private persons in any country, by employees and persons associated with the company in order to obtain or retain business or a business advantage for the company. Liability is strict, with no element of a corrupt state of mind, but a defense of having in place adequate procedures designed to prevent bribery is available. As described above, our business is heavily regulated and therefore involves significant interaction with government officials in many countries. Additionally, in certain countries, the health care providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, our dealings with these prescribers and purchasers may be subject to the FCPA, the U.K. Bribery Act and similar laws. Recently the Securities and Exchange Commission, or SEC, and the DOJ have increased their FCPA enforcement activities with respect to pharmaceutical companies. In addition, under the Dodd-Frank Wall Street Reform and Consumer Protection Act, private individuals who report to the SEC original information that leads to successful enforcement actions may be eligible for a monetary award. We engage in ongoing efforts designed to ensure our compliance with these laws, including due diligence, training, policies, procedures, and internal controls. However, there is no certainty that all employees and third party business partners (including our distributors, wholesalers, agents, contractors, and other partners) will comply with anti-bribery laws. In particular, we do not control the actions of our suppliers and other third party agents, although we may be liable for their actions. Violation of these laws may result in civil or criminal sanctions, which could include monetary fines, criminal penalties, and disgorgement of past profits.

Data Protection and Privacy

We are subject to data protection and privacy laws and regulations globally, which restrict the processing of personal data. The legislative and regulatory landscape for privacy and data security continues to evolve with an increased attention in countries globally that could potentially affect our business. In particular, we are subject to the EU General Data Protection Regulation, which imposes penalties up to 4% of annual global revenue, and the California Consumer Privacy Act of 2018. These laws and regulations applicable to our business, increase potential enforcement and litigation activity. In order to manage these evolving risks, we have adopted a global privacy program that governs the processing of personal data across our business.

Marketing Exclusivity

The Hatch-Waxman Act

The marketing approval process described above for the U.S. is premised on the applicant being the owner of, or having obtained a right of reference to, all of the data required to prove the safety and effectiveness of a drug product. This type of marketing application, sometimes referred to as a "full" or "stand-alone" NDA, is governed by Section 505(b)(1) of the United States Federal Food, Drug, and Cosmetic Act, or FDCA. A Section 505(b)(1) NDA contains full reports of investigations of safety and effectiveness, which includes the results of preclinical and clinical trials, together with detailed information on the manufacture and composition of the product, in addition to other information. As an alternative, the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, provides two abbreviated approval pathways for certain drug products.

The first path, under Section 505(b)(2) of the FDCA, usually is used for the approval of a product that is similar, but not identical, to a previously-approved brand-name product, referred to as the reference listed drug, or RLD. Under this path, the applicant is permitted to rely to some degree on FDA's finding that the RLD is safe and effective and must submit its own product-specific data on safety and effectiveness only to the extent necessary to bridge the differences between the products. The second abbreviated path established under the Hatch-Waxman Act is for the approval of generic drugs. Section 505(j) of the FDCA permits the submission of an ANDA for a generic version of an approved, brand-name drug. Generally, an ANDA must contain data and information showing that the proposed generic product and the RLD (i) have the same active ingredient, in the same strength and dosage form, to be delivered via the same route of administration, (ii) are intended for the same uses, and (iii) are bioequivalent. This data and information are provided instead of data and information independently demonstrating the proposed generic product's safety and effectiveness.

The Hatch-Waxman Act requires an ANDA or a Section 505(b)(2) NDA applicant to certify that there are no patents listed for that product in the Orange Book, or that for each Orange Book-listed patent either the listed patent has expired, the listed patent will expire on a particular date and approval is sought after patent expiration, or the listed patent is invalid or will not be infringed by the manufacture, use or sale of the new product. A certification that approval is sought after patent expiration is called a "Paragraph III Certification." A certification that the new product will not infringe the RLD's Orange Book-listed patents, or that such patents are invalid, is called a "Paragraph IV Certification." If a relevant patent covers an approved method of use, an ANDA or Section 505(b)(2) NDA applicant can also file a statement, called, in the case of an ANDA, a "section viii statement," that the application does not seek approval of the method of use covered by the listed patent. With such a statement, the applicant must "carve out" the protected method of use (typically an indication and related material) from the proposed product's labeling. If the applicant makes a Paragraph III Certification, the ANDA or the Section 505(b)(2) NDA will not be approved until the listed patents claiming the RLD have expired.

If the applicant has provided a Paragraph IV Certification to FDA, the applicant must also send a notice of that certification to the NDA holder and the relevant patent holders once FDA accepts the ANDA or the Section 505(b)(2) NDA for filing. The NDA and patent holders then have 45 days to initiate a patent infringement lawsuit. Filing the lawsuit triggers an automatic stay on FDA's approval of the ANDA or the Section 505(b)(2) NDA until the earliest of 30 months after the NDA holder's receipt of the notice of Paragraph IV Certification, expiration of the patent, certain settlements of the lawsuit, or a decision in the infringement case that is favorable to the applicant. FDA may issue tentative approval of an application if the application meets all conditions for approval but cannot receive effective approval because the 30-month stay or another period of regulatory exclusivity has not expired. If an ANDA or Section 505(b)(2) NDA is approved before conclusion of any relevant patent litigation, the applicant can choose to launch the product, but does so "at risk" of being liable for damages, and potentially treble damages, if the RLD sponsor or patent holder ultimately prevails in patent litigation.

Under the Hatch-Waxman Act, newly approved drugs and indications may benefit from statutory periods of non-patent marketing exclusivity that can potentially delay review or approval of an ANDA or Section 505(b)(2) application. For example, the Hatch-Waxman Act provides five-year marketing exclusivity to the first applicant to gain approval of an NDA for a new chemical entity, meaning a drug containing an active moiety that FDA has not previously approved. During this period, FDA cannot accept for review an ANDA or a Section 505(b)(2) NDA for a product containing the same moiety, except that an application containing a Paragraph IV Certification may be submitted after four years, which may trigger the litigation and stay described above. The Hatch-Waxman Act also provides three years of marketing exclusivity with the approval of an NDA, including a Section 505(b)(2) NDA, for a product containing a previously-approved moiety but that incorporates a change (such as a new indication, dosage form or strength) from an approved product with the same moiety, if the change required clinical data from new investigations that were conducted or sponsored by the applicant. This three-year exclusivity does not preclude submission of the ANDA or Section 505(b)(2) NDA for such a product, but prevents FDA from giving final approval to such product.

The Hatch-Waxman Act also permits a patent term extension of up to five years (but not beyond 14 years from the date of approval) for an NDA, including a Section 505(b)(2) NDA, that is approved for a product that contains an active ingredient that has not previously been approved. The extension, which compensates for patent term lost during product development and FDA regulatory review process, is generally equal to the sum of one-half the time between the effective date of an IND application and the submission date of an NDA, and all of the time between the submission date of an NDA and the approval of that application. It is available for only one patent for a given product, and it must be a patent that claims the product or a method of using or manufacturing the product. The USPTO, in consultation with FDA, reviews and approves applications for patent term extension.

In the EU, innovative medicinal products that are subject to marketing authorization on the basis of a full dossier qualify for eight years' data exclusivity upon marketing authorization and an additional two years' market exclusivity. Data exclusivity prevents regulatory authorities in the EU from referencing the innovator's data to assess a generic application or biosimilar application for eight years from the date of authorization of the innovative product, after which a generic or biosimilar marketing authorization application can be submitted, and the innovator's data may be referenced. However, the generic

product or biosimilar products cannot be marketed in the EU for a further two years thereafter. The overall ten-year period may be extended for a further year to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies.

Orphan Drug and Other Exclusivities

Some jurisdictions, including the U.S., may designate drugs or biologics for relatively small patient populations as orphan drugs. FDA grants orphan drug designation to drugs or biologics intended to treat a rare disease or condition, which is one that affects fewer than 200,000 individuals in the U.S., or more than 200,000 individuals, but for which there is no reasonable expectation that the cost of developing the product and making it available in the U.S. for the disease or condition will be recovered from U.S. sales of the product. Orphan drug designation does not shorten the duration of the regulatory review process or lower the approval standards, but can provide important benefits, including consultation with FDA. If a product is approved for its orphan designated use, it may be entitled to ODE, which blocks FDA from approving for seven years any other application for a product that is the same drug for the same indication. If there is a previously-approved product that is the same drug for the same indication, orphan drug designation requires the sponsor to provide a plausible hypothesis of clinical superiority over the approved product, whereas ODE requires the sponsor to actually demonstrate clinical superiority. Clinical superiority can be established by way of greater efficacy, greater safety, or making a major contribution to patient care. Additionally, a later product can be approved if the sponsor holding ODE consents, or cannot adequately supply the market. ODE does not prevent approval of another sponsor's application for different indications or uses of the same drug, or for different drugs for the same indication. Defibrotide has been granted ODE by FDA to treat and prevent VOD until March 2023. Vyxeos has been granted ODE by FDA for the treatment of AML until August 2024. Epidiolex has received ODE to treat seizures associated with LGS and DS through 2025 and TSC through 2027. In June 2021, FDA, recognized seven years of ODE for Xywav stating that Xywav is clinically superior to Xyrem by means of greater safety due to reduced chronic sodium burden. Xywav has been granted ODE by FDA to treat narcolepsy through 2027 and to treat IH through 2028. Rylaze has been granted ODE for the treatment of patients with ALL or LBL until 2028.

Biologic products approved under a BLA are subject to the Biologics Price Competition and Innovation Act, or BPCIA, which authorizes an abbreviated approval pathway for a biological product that is "biosimilar" to an already approved biologic, or reference product. The BPCIA provides periods of exclusivity that protect a reference product from competition by biosimilars. FDA may not accept a biosimilar application for review until four years after the date of first licensure of the reference product, and the biosimilar cannot be licensed until 12 years after the reference product was first licensed.

Under certain circumstances, the exclusivity periods applicable to drugs and biologics and the patent-related protections applicable to drugs may be eligible for a six-month extension if the sponsor submits pediatric data that fairly respond to a written request from FDA for such data. This exclusivity may be granted even if the data does not support a pediatric indication. We consider seeking pediatric exclusivity for our products whenever appropriate. For example, in response to a written request from FDA, we conducted a Phase 3 clinical trial to assess the safety and efficacy of Xyrem in children and adolescents aged seven to 17 who have narcolepsy with cataplexy, and submitted study results in a supplement to the Xyrem NDA, seeking approval for this indication. In October 2018, FDA approved the sNDA and notified us that we had been granted pediatric exclusivity, extending by six months the preclusive effect of our Orange Book-listed patents for Xyrem, as well as the three-year regulatory exclusivity period granted to the Xyrem pediatric indication because of the clinical studies that were necessary for approval of the sNDA.

In the EU, orphan drug designation may be granted to products that can be used to treat life-threatening diseases or chronically debilitating conditions with an incidence of no more than five in 10,000 people or that, for economic reasons, would be unlikely to be developed without incentives. Orphan designated medicinal products are entitled to a range of benefits during the development and regulatory review process and ten years of market exclusivity in all EU member states upon approval. As in the U.S., a similar medicinal product with the same orphan indication may be approved, notwithstanding orphan product exclusivity, if the exclusivity holder gives consent or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if the similar product is deemed safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity granted in relation to the original orphan medicinal product may, in addition, be reduced to six years if it can be demonstrated, on the basis of available evidence, that the original orphan medicinal product is sufficiently profitable not to justify maintenance of market exclusivity. Defibrotide has been granted orphan drug designation by the EC for the treatment of VOD and prevention of GvHD until October 2023, by the Korean Ministry of Food and Drug Safety to treat and prevent VOD, and by the Commonwealth of Australia-Department of Health for the treatment of VOD. Vyxeos has been granted orphan drug designation by the EC until August 2028. We also received Orphan Designation from EMA's Committee for Orphan Medicinal Products, or COMP, for Epidyolex for DS, LGS and TSC, and the COMP reconfirmed the designation for DS, LGS and TSC upon EC's approval.

Pharmaceutical Pricing, Reimbursement by Government and Private Payors and Patient Access

Pricing and Reimbursement

Successful commercialization of our products depends in significant part on adequate financial coverage and reimbursement from third party payors, including governmental payors (such as the Medicaid and Medicare programs in the U.S.), managed care organizations and private health insurers. Third party payors decide which drugs will be reimbursed and establish reimbursement and co-pay levels and conditions for reimbursement. Third party payors are increasingly challenging the prices charged for medical products and services by examining their cost effectiveness, as demonstrated in pharmacoeconomic and/or clinical studies, in addition to their safety and efficacy. In some cases, for example, third party payors try to encourage the use of less expensive products, when available, through their prescription benefits coverage and reimbursement, co-pay and prior authorization policies. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third party payors may require prior approval before covering a specific product, or may require patients and health care providers to try other covered products first. Third party payors may also limit coverage to specific products on an approved list, or formulary, which might not include all of the approved products for a particular indication. For certain categories of products, third party payors, principally through contracted pharmacy benefit managers, or PBMs, negotiate rebates with drug manufacturers for inclusion of products on their formularies in specific positions or coverage criteria. Beginning in the third quarter of 2019, we have been entering into agreements with certain PBMs to provide rebates for our products where coverage was provided and products were listed in certain formulary positions, among other conditions.

Medicaid is a joint federal and state program that is administered by the states for low-income and disabled beneficiaries. Medicare is a federal program that is administered by the federal government covering individuals age 65 and over as well as those with certain disabilities. Medicare Part B pays physicians who administer our products. Under the Medicaid Drug Rebate Program, as a condition of having federal funds made available to the states for our drugs under Medicare Part B, we are required to pay a rebate to each state Medicaid program for our covered outpatient drugs that are dispensed to Medicaid beneficiaries and paid for by a state Medicaid program. Medicaid rebates are based on pricing data we report on a monthly and quarterly basis to the U.S. Centers for Medicare & Medicaid Services, or CMS, the federal agency that administers the Medicaid Drug Rebate Program and Medicare. These data include the average manufacturer price and, in the case of innovator products, the best price for each drug which, in general, represents the lowest price available from the manufacturer to any entity in the U.S. in any pricing structure, calculated to include all applicable sales and associated rebates, discounts and other price concessions. If we become aware that our reporting for a prior quarter was incorrect, or has changed as a result of recalculation of the pricing data, we are obligated to resubmit the corrected data for up to three years after those data originally were due. We are required to provide average sales price, or ASP, information for certain of our products to CMS on a quarterly basis. The ASP is calculated based on a statutorily defined formula as well as regulations and interpretations of the statute by CMS. This information is used to compute Medicare payment rates, with rates for Medicare Part B drugs outside the hospital outpatient setting and in the hospital outpatient setting consisting of ASP plus a specified percentage.

Federal law requires that any company that participates in the Medicaid Drug Rebate Program also participate in the Public Health Service's 340B program, or the 340B program, in order for federal funds to be available for the manufacturer's drugs under Medicaid and Medicare Part B. The 340B program, which is administered by the Health Resources and Services Administration, or HRSA, requires participating manufacturers to agree to charge statutorily defined covered entities no more than the 340B "ceiling price" for the manufacturer's covered drugs used in an outpatient setting. These 340B covered entities include certain qualifying community health clinics, a variety of entities that receive health services grants from the Public Health Service, and multiple categories of hospitals, including children's hospitals, critical access hospitals, free standing cancer hospitals and hospitals that serve a disproportionate share of low-income patients. The 340B ceiling price is calculated using a statutory formula, which is based on the average manufacturer price and rebate amount for the covered outpatient drug as calculated under the Medicaid Drug Rebate Program, and in general, products subject to Medicaid price reporting and rebate liability are also subject to the 340B ceiling price calculation and discount requirement. A regulation regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities became effective on January 1, 2019. We also are required to report our 340B ceiling prices to HRSA on a quarterly basis and HRSA then publishes them to 340B covered entities. In addition, legislation may be introduced that, if passed, would further expand the 340B program to additional covered entities or would require participating manufacturers to agree to provide 340B discounted pricing on drugs used in an inpatient setting.

A provision in The American Rescue Plan Act of 2021 eliminates, effective January 2024, the statutory cap on rebates drug manufacturers are required to pay under the Medicaid Drug Rebate Program. Since 2010, the total Medicaid rebate amount a drug manufacturer is required to pay under the Medicaid Drug Rebate Program has been capped at 100 percent of the Average Manufacturer Price. The elimination of the cap on rebates means that manufacturer discounts to Medicaid may rise beginning in 2024 and, in certain circumstances, rebates could exceed the amount that state Medicaid programs pay for the

drug. This policy change will have the greatest impact on drugs whose prices have reached the 100 percent Average Manufacturer Price rebate cap.

Effective January 2023, a provision of the Infrastructure Investment and Jobs Act requires a manufacturer of single source drugs or biologicals in single-use packages or single dose containers to pay a refund on discarded amounts of drug under Medicare Part B where the discarded amount exceeds an applicable threshold.

In order to be eligible to have our products paid for with federal funds under the Medicaid and Medicare Part B programs and purchased by certain federal agencies and grantees, we also participate in the U.S. Department of Veterans Affairs, or VA, Federal Supply Schedule, or FSS, pricing program. Under this program, we are obligated to make our products available for procurement on an FSS contract under which we must comply with standard government terms and conditions and charge a price to certain federal agencies that is no higher than the statutory Federal Ceiling Price, or FCP. The FCP is based on the non-federal average manufacturer price, or Non-FAMP, which we calculate and report to the VA on a quarterly and annual basis. We also participate in the Tricare Retail Pharmacy program, under which we pay quarterly rebates on utilization of innovator products that are dispensed through the Tricare Retail Pharmacy network to Tricare beneficiaries. The rebates are calculated as the difference between the annual Non-FAMP and FCP. Pricing and rebate calculations vary across products and programs, are complex, and are often subject to interpretation by us, governmental or regulatory agencies and the courts, which can change and evolve over time.

In addition, in the U.S., drug pricing by pharmaceutical companies is currently, and is expected to continue to be, under close scrutiny, including with respect to companies that have increased the price of products after acquiring those products from other companies. There are numerous ongoing efforts at the federal and state level seeking to indirectly or directly regulate drug prices to reduce overall healthcare costs using tools such as price ceilings, value-based pricing and increased transparency and disclosure obligations. Several states have passed or are considering legislation that requires or purports to require companies to report pricing information, including proprietary pricing information. For example, in 2017, California adopted a prescription drug price transparency state bill requiring advance notice of and an explanation for price increases of certain drugs that exceed a specified threshold. Similar bills have been previously introduced at the federal level and additional legislation could be introduced this year.

Similar to what is occurring in the U.S., political, economic and regulatory developments outside of the U.S. are also subjecting the healthcare industry to fundamental changes and challenges. Pressure by governments and other stakeholders on prices and reimbursement levels continue to exist. In various EU member states we expect to be subject to continuous cost-cutting measures, such as lower maximum prices, lower or lack of reimbursement coverage and incentives to use cheaper, usually generic, products as an alternative. Health technology assessment, or HTA, of medicinal products is becoming an increasingly common part of the pricing and reimbursement procedures in some EU member states, including countries representing major markets. The HTA process, which is governed by the national laws of these countries, is the procedure according to which the assessment of the public health impact, therapeutic impact and the economic and societal impact of use of a given medicinal product in the national healthcare systems of the individual country is conducted. HTA generally compares attributes of individual medicinal products, as compared with other treatment options available on the market. The outcome of HTA regarding specific medicinal products will often influence the pricing and reimbursement status granted to these medicinal products by the competent authorities of individual EU member states. In December 2021, the EC adopted a HTA regulation intended to boost cooperation among EU member states in assessing health technologies, including new medicinal products. The regulation will apply to all EU member states from January 2025 provides that EU member states will be able to use common HTA tools, methodologies, and procedures across the EU. Individual EU member states will continue to be responsible for drawing conclusions on the overall value of a new health technology for their healthcare system, and pricing and reimbursement decisions.

In the EU, our products are marketed through various channels and within different legal frameworks. The making available or placing on the EU market of unauthorized medicinal products is generally prohibited. However, the competent authorities of the EU member states may exceptionally and temporarily allow and reimburse the supply of such unauthorized products, either on a named patient basis or through a compassionate use process, to individual patients or a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorized medicinal product. Such reimbursement may no longer be available if authorization for named patient or compassionate use programs expire or is terminated or if marketing authorization is granted for the product. In some EU member states, authorization and reimbursement policies may also delay commercialization of our products, or may adversely affect our ability to sell our products on a profitable basis. After initial price and reimbursement approvals, reductions in prices and changes in reimbursement levels can be triggered by multiple factors, including reference pricing systems and publication of discounts by third party payors or authorities in other countries. In the EU, prices can be reduced further by parallel distribution and parallel trade, or arbitrage between low-priced and high-priced EU member states.

For more information, including with respect to recent legal developments regarding the Medicaid Drug Rebate Program, Medicare Part B, and the 340B program, see the risk factors under the headings “*Adequate coverage and reimbursement from*

third party payors may not be available for our products and we may be unable to successfully contract for coverage from pharmacy benefit managers and group purchasing organizations, which could diminish our sales or affect our ability to sell our products profitably; conversely, to secure coverage from these organizations, we may be required to pay rebates or other discounts or other restrictions to reimbursement that could diminish our sales," "The pricing of pharmaceutical products has come under increasing scrutiny as part of a global trend toward healthcare cost containment and resulting changes in healthcare law and policy may impact our business in ways that we cannot currently predict, which could have a material adverse effect on our business and financial condition" and *"If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs, we could be subject to additional reimbursement requirements, penalties, sanctions and fines, which could have a material adverse effect on our business, financial condition, results of operations and growth prospects"* in Part I, Item 1A of this Annual Report on Form 10-K.

Patient Copay Assistance and Free Product Programs

We have various patient programs to help patients access and pay for our products, including co-pay coupons for certain products, services that help patients determine their insurance coverage for our products, and a free product program. We also make grants to independent charitable foundations that help financially needy patients with their premium, and co-pay and co-insurance obligations. There has been enhanced scrutiny of company-sponsored patient assistance programs, including co-pay assistance programs and donations to third-party charities that provide such assistance, as well as reimbursement support offerings.

The OIG has established guidelines for pharmaceutical manufacturers who make donations to charitable organizations providing co-pay assistance to Medicare patients. Such donations are unlikely to run afoul of the anti-kickback laws provided that the organizations receiving donations, among other things, are *bona fide* charities, are entirely independent of and not controlled by the manufacturer, provide aid to applicants on a first-come basis according to consistent financial criteria, and do not link aid to use of a donor's product. In 2016 and 2017, we received subpoenas from the U.S. Attorney's Office for the District of Massachusetts requesting documents related to our support of charitable organizations that provide financial assistance to Medicare patients. In April 2019, we finalized our civil settlement agreement with the DOJ and OIG, and entered into a corporate integrity agreement requiring us to maintain our ongoing corporate compliance program and obligating us to implement or continue, as applicable, a set of defined corporate integrity activities to ensure compliance with OIG's policies around charitable contributions for a period of five years from the effective date of the corporate integrity agreement.

About Jazz Pharmaceuticals plc

Jazz Pharmaceuticals plc was formed under the laws of Ireland (registered number 399192) as a private limited liability company in March 2005 under the name Azur Pharma Limited and was subsequently re-registered as a public limited company under the name Azur Pharma Public Limited Company, or Azur Pharma, in October 2011. On January 18, 2012, the businesses of Jazz Pharmaceuticals, Inc. and Azur Pharma were combined in a merger transaction, in connection with which Azur Pharma was re-named Jazz Pharmaceuticals plc and we became the parent company of and successor to Jazz Pharmaceuticals, Inc.

Our predecessor, Jazz Pharmaceuticals, Inc., was incorporated in California in March 2003 and was reincorporated in Delaware in January 2004.

Available Information

The mailing address of our headquarters is Fifth Floor, Waterloo Exchange, Waterloo Road, Dublin 4, Ireland, and our telephone number at that location is 353-1-634-7800. Our website is www.jazzpharmaceuticals.com.

We file or furnish pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, as applicable, our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, amendments to those reports, proxy statements and other information electronically with the SEC. Through a link on our website, we make copies of our periodic and current reports, amendments to those reports, proxy statements and other information available, free of charge, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. Information found on, or accessible through, our website is not a part of, and is not incorporated into, this Annual Report on Form 10-K.

Item 1A. Risk Factors

We have identified the following risks and uncertainties that may have a material adverse effect on our business, financial condition or results of operations. The risks described below are not the only ones we face. Additional risks not presently known to us or that we currently believe are immaterial may also significantly impair our business operations. Our business could be harmed by any of these risks. The trading price of our ordinary shares could decline due to any of these risks, and you may lose all or part of your investment. In assessing these risks, you should also refer to the other information contained in this Annual Report on Form 10-K, including our consolidated financial statements and accompanying notes.

Risks Related to Our Lead Products and Product Candidates

Our inability to maintain or increase sales from our oxybate franchise would have a material adverse effect on our business, financial condition, results of operations and growth prospects.

Our business has been substantially dependent on Xyrem® (sodium oxybate) oral solution, and our financial results have been significantly influenced by sales of Xyrem. Our future plans assume that Xywav®, our oxybate product launched in November 2020 with 92%, or approximately 1,000 to 1,500 milligrams per day, less sodium than Xyrem, depending on the dose, absence of a sodium warning and dosing titration option, will become the treatment of choice for patients who can benefit from oxybate treatment, current Xyrem patients, and patients who previously were not prescribed Xyrem, including those patients for whom sodium content is a concern. In June 2021, U.S. Food and Drug Administration, or FDA, recognized seven years of Orphan Drug Exclusivity through July 21, 2027 for Xywav in narcolepsy stating that Xywav is clinically superior to Xyrem by means of greater safety due to reduced chronic sodium burden. Our ability to successfully commercialize Xywav will depend on, among other things, our ability to maintain adequate coverage and reimbursement for Xywav and acceptance of Xywav by payors, physicians and patients.

Our ability to maintain or increase oxybate product sales and realize the anticipated benefits from our investment in Xywav is subject to a number of additional risks and uncertainties as discussed in greater detail below, including those related to the near-term introduction of authorized generic and generic versions of sodium oxybate and new products for treatment of cataplexy and/or excessive daytime sleepiness, or EDS, in narcolepsy in the U.S. market; the current and potential impacts of the COVID-19 pandemic, including the current and expected future negative impact on demand for our products and the uncertainty with respect to our ability to meet commercial demand in the future; increased pricing pressure from, changes in policies by, or restrictions on reimbursement imposed by, third party payors, including our ability to maintain adequate coverage and reimbursement for Xywav; and challenges to our intellectual property around Xyrem and/or Xywav. While we expect that our business will continue to be substantially dependent on oxybate product sales, there is no guarantee that we can maintain oxybate sales at or near historical levels, or that oxybate sales will continue to grow. A significant decline in oxybate sales could cause us to reduce our operating expenses or seek to raise additional funds, which would have a material adverse effect on our business, financial condition, results of operations and growth prospects, including on our ability to acquire, in-license or develop new products to grow our business.

The introduction of new products in the U.S. market that compete with, or otherwise disrupt the market for, our oxybate products and product candidates would adversely affect sales of our oxybate products and product candidates.

While Xywav and Xyrem are currently the only products approved by FDA and marketed in the U.S. for the treatment of both cataplexy and EDS in both adult and pediatric patients with narcolepsy, new treatment options for cataplexy and EDS in narcolepsy have launched, and in the future, other products may be launched that are competitive with or disrupt the market for our oxybate products.

For example, in the future, we expect Xywav and Xyrem to face competition from authorized generic and generic versions of sodium oxybate. Nine companies have sent us notices that they had filed abbreviated new drug applications, or ANDAs, seeking approval to market a generic version of Xyrem, and we have filed and settled patent lawsuits with all nine companies. To date, FDA has approved or tentatively approved four of these ANDAs, and we believe that it is likely that FDA will approve or tentatively approve some or all of the others. In our patent litigation settlement with the first filer, West-Ward Pharmaceuticals Corp. (a wholly owned subsidiary of Hikma Pharmaceuticals PLC and now known as Hikma in the U.S.), or Hikma, we granted Hikma the right to sell an authorized generic product, or AG Product, with royalties back to us, in the U.S. beginning on January 1, 2023, or earlier under certain circumstances. Hikma has a right to elect to continue to sell the Hikma AG Product for a total of up to five years. We also granted Hikma a license to launch its own generic sodium oxybate product as early as six months after it has the right to sell the Hikma AG Product, but if it elects to launch its own generic product, Hikma will no longer have the right to sell the Hikma AG Product. In our settlements with Amneal Pharmaceuticals LLC, or Amneal, Lupin Inc., or Lupin, and Par Pharmaceutical, Inc., or Par, we granted each party the right to sell a limited volume of an AG Product in the U.S. beginning on July 1, 2023, or earlier under certain circumstances, and ending on December 31, 2025, with royalties back to us. AG Products will be distributed through the same risk evaluation and mitigation strategy, or REMS, as Xywav and Xyrem. We also granted each of Amneal, Lupin and Par a license to launch its own generic sodium oxybate product under its ANDA on or after December 31, 2025, or earlier under certain circumstances, including the circumstance where Hikma elects to launch its own generic product. If Amneal, Lupin or Par elects to launch its own generic product under such circumstance, it will no longer have the right to sell an AG Product. In our settlements with each of the other five ANDA filers, we granted each a license to launch its own generic sodium oxybate product under its ANDA on or after December 31, 2025, or earlier under certain circumstances, including circumstances where Hikma launches its own generic sodium oxybate product. The actual timing of the launch of an AG Product or generic sodium oxybate product is uncertain because the launch dates of the AG Products and generic sodium oxybate products under our settlement agreements are subject to acceleration under certain circumstances. It is possible that additional companies may file ANDAs seeking to market a generic version of Xyrem which could lead to additional patent litigation or challenges with respect to Xyrem.

Any ANDA holder launching an AG Product or another generic sodium oxybate product will independently establish the price of the AG Product and/or its own generic sodium oxybate product. Generic competition often results in decreases in the prices at which branded products can be sold. After any introduction of a generic product, whether or not it is an AG Product, a significant percentage of the prescriptions written for Xyrem will likely be filled with the generic product. Certain U.S. state laws allow for, and in some instances in the absence of specific instructions from the prescribing physician mandate, the dispensing of generic products rather than branded products when a generic version is available. This would result in reduction in sales of, and revenue from, Xyrem, although we would continue to receive royalties and other revenue based on sales of an AG Product in accordance with the terms of our settlement agreements.

A circumstance that could trigger acceleration of Hikma's launch date for an AG Product, which would also accelerate Amneal, Lupin and Par's launch dates for their AG Products and ultimately could lead to acceleration of the other settling ANDA filers' launch dates for their generic sodium oxybate products, is a substantial reduction in Xyrem net sales. Such a reduction could occur under various circumstances, including from our sales of Xywav or if a third party introduces a product to treat EDS or cataplexy in narcolepsy that leads to a substantial decline in Xyrem net sales. Accordingly, our strategy to drive revenue growth in our key franchises through, among other things, rapid adoption and broad access of Xywav in the U.S. could lead to the acceleration of such launch dates. Other companies may develop a sodium oxybate product for treatment of narcolepsy, using an alternative formulation or a different delivery technology, and seek approval in the U.S. using a new drug application, or NDA, approval pathway under Section 505(b)(2) and referencing the safety and efficacy data for Xyrem. In February 2021, FDA accepted for filing an NDA submitted by Avadel Pharmaceuticals plc, or Avadel, for an extended-release formulation of sodium oxybate which uses its proprietary technology for the treatment of EDS and cataplexy in patients with narcolepsy with a Prescription Drug User Fee Act, or PDUFA, target action date of October 15, 2021. On October 15, 2021, Avadel announced that FDA review is ongoing and FDA will likely not take action in October 2021 and will provide a new target action date. Xyrem may also face increased competition from new branded entrants to treat EDS in narcolepsy such as pitolisant. Other companies have announced that they have product candidates in various phases of development to treat the symptoms of narcolepsy, such as Axsome Therapeutics, Inc.'s reboxetine, and various companies are performing research and development on orexin agonists for the treatment of sleep disorders.

We expect that Xywav for the treatment of both cataplexy and EDS in patients with narcolepsy will face competition similar to that described above for Xyrem, including from generic or authorized generic sodium oxybate products or new branded entrants in narcolepsy notwithstanding FDA recognizing Orphan Drug Exclusivity for Xywav. For example, we received notice in June 2021 that Lupin filed an ANDA for a generic version of Xywav. Additional companies may file ANDAs seeking to market a generic version of Xywav which could lead to additional patent litigation or challenges with respect to Xywav. Moreover, Avadel has announced that it has obtained an orphan drug designation from FDA for its extended-release sodium oxybate formulation. To obtain approval with Orphan Drug Exclusivity, Avadel will have to show clinical superiority to Xywav and Xyrem. We cannot predict the timing or approvability of Avadel's sodium oxybate product candidate or how FDA will evaluate any clinical superiority arguments that either we or Avadel may make, but in any event, we expect to face competition from Avadel, if its product candidate is approved.

Moreover, non-oxybate products intended for the treatment of EDS or cataplexy in narcolepsy, including new market entrants, even if not directly competitive with Xywav or Xyrem, could have the effect of changing treatment regimens and payor or formulary coverage of Xywav or Xyrem in favor of other products, and indirectly materially and adversely affect sales of Xywav and Xyrem. To date, we have not seen a material impact to our business from the introduction of these new market entrants. Examples of such new market entrants include our product, Sunosi, and pitolisant, a drug that was approved by FDA in 2019 for the treatment of EDS in adult patients with narcolepsy and approved by FDA in October 2020 pursuant to a complete response resubmission for an adult cataplexy indication in the U.S. Pitolisant has also been approved and marketed in Europe to treat adult patients with narcolepsy, with or without cataplexy, and to treat EDS in obstructive sleep apnea, or OSA. In addition, we are also aware that prescribers often prescribe branded or generic medications for cataplexy, before or instead of prescribing oxybate therapy in Xywav and Xyrem, and that payors often require patients to try such medications before they will cover Xywav or Xyrem, even if they are not approved for this use. Examples of such products are described in "Business—Competition" in Part I, Item 1 of this Annual Report on Form 10-K.

We expect that the approval and launch of an AG Product or other generic version of Xyrem could have a material adverse effect on our sales of Xywav and Xyrem and on our business, financial condition, results of operations and growth prospects. We also expect that sales of Xywav will, and the approval and launch of any other sodium oxybate (including Avadel's extended-release sodium oxybate formulation) or alternative product that treats narcolepsy could, have a material adverse effect on our sales of Xyrem, which could have the additional impact of potentially triggering acceleration of market entry of AG Products or other generic sodium oxybate products under our patent litigation settlement agreements.

The distribution and sale of our oxybate products are subject to significant regulatory restrictions, including the requirements of a REMS and safety reporting requirements, and these regulatory and safety requirements subject us to risks and uncertainties, any of which could negatively impact sales of Xywav and Xyrem.

The active pharmaceutical ingredient, or API, of Xywav and Xyrem, is a form of gamma-hydroxybutyric acid, or GHB, a central nervous system depressant known to be associated with facilitated sexual assault as well as with respiratory depression and other serious side effects. As a result, FDA requires that we maintain a REMS with elements to assure safe use, or ETASU, for Xywav and Xyrem to help ensure that the benefits of the drug in the treatment of cataplexy and EDS in narcolepsy outweigh the serious risks of the drug. The REMS imposes extensive controls and restrictions on the sales and marketing of Xywav and Xyrem that we are responsible for implementing. Any failure to demonstrate our substantial compliance with our REMS obligations, including as a result of business or other interruptions resulting from the evolving effects of the COVID-19 pandemic, or a determination by FDA that the REMS is not meeting its goals, could result in enforcement action by FDA, lead to changes in our REMS obligations, negatively affect sales of Xywav or Xyrem, result in additional costs and expenses for us and/or require us to invest a significant amount of resources, any of which could materially and adversely affect our business, financial condition, results of operations and growth prospects.

FDA has stated that it will evaluate the Xywav and Xyrem REMS on an ongoing basis and will require modifications as may be appropriate. We cannot predict whether FDA will request, seek to require or ultimately require modifications to, or impose additional requirements on, the Xywav and Xyrem REMS, including in connection with the submission of new oxybate products or indications, the introduction of authorized generics, or to accommodate generics, or whether FDA will approve modifications to the Xywav and Xyrem REMS that we consider warranted. Any modifications approved, required or rejected by FDA could change the safety profile of Xywav or Xyrem, and have a significant negative impact in terms of product liability, public acceptance of Xywav or Xyrem as a treatment for cataplexy and EDS in narcolepsy, and prescribers' willingness to prescribe, and patients' willingness to take, Xywav or Xyrem, any of which could have a material adverse effect on our oxybate business. Modifications approved, required or rejected by FDA could also make it more difficult or expensive for us to distribute Xywav or Xyrem, make distribution easier for oxybate competitors, disrupt continuity of care for Xywav or Xyrem patients and/or negatively affect sales of Xywav or Xyrem.

We depend on outside vendors, including Express Scripts Specialty Distribution Services, Inc., the central certified pharmacy, to distribute Xywav and Xyrem in the U.S., provide patient support services and implement the requirements of the Xywav and Xyrem REMS. If the central pharmacy fails to meet the requirements of the Xywav and Xyrem REMS applicable to the central pharmacy or otherwise does not fulfill its contractual obligations to us, moves to terminate our agreement, refuses or fails to adequately serve patients, or fails to promptly and adequately address operational challenges or challenges in implementing REMS modifications, whether due to business or other interruptions resulting from the evolving effects of the COVID-19 pandemic or otherwise, the fulfillment of Xywav or Xyrem prescriptions and our sales would be adversely affected. If we change to a new central pharmacy, new contracts might be required with government payors and other insurers who pay for Xywav or Xyrem, and the terms of any new contracts could be less favorable to us than current agreements. In addition, any new central pharmacy would need to be registered with the U.S. Drug Enforcement Administration, or DEA, and certified under the REMS and would also need to implement the particular processes, procedures and activities necessary to distribute under the Xywav and Xyrem REMS. Transitioning to a new pharmacy could result in product shortages, which would negatively affect sales of Xywav and Xyrem, result in additional costs and expenses for us and/or take a significant amount of time, any of which could materially and adversely affect our business, financial condition, results of operations and growth prospects.

In its approval of Hikma's ANDA, FDA waived the requirement of a single shared REMS between the brand drug and generic versions, approving Hikma's ANDA with a generic sodium oxybate REMS separate from the Xywav and Xyrem REMS, except for the requirement that the generic sodium oxybate REMS program pharmacies contact the Xywav and Xyrem REMS by phone to verify and report certain information. The generic sodium oxybate REMS was approved with the condition that it be open to all future sponsors of ANDAs or NDAs for sodium oxybate products. A sodium oxybate distribution system that is less restrictive than the Xywav and Xyrem REMS, such as the generic sodium oxybate REMS, which provides that generic sodium oxybate products and potentially new sodium oxybate products approved under a Section 505(b)(2) NDA approval pathway could be distributed through multiple pharmacies, could increase the risks associated with oxybate distribution. Because patients, consumers and others may not differentiate generic sodium oxybate from Xyrem or differentiate between the different REMS programs, any negative outcomes, including risks to the public, caused by or otherwise related to a separate sodium oxybate REMS, could have a significant negative impact in terms of product liability, our reputation and good will, public acceptance of Xywav or Xyrem as a treatment for cataplexy and EDS in narcolepsy, and prescribers' willingness to prescribe, and patients' willingness to take, Xywav or Xyrem, any of which could have a material adverse effect on our oxybate business.

We may face pressure to further modify the Xywav and Xyrem REMS or to license or share intellectual property pertinent to that REMS, including proprietary data required for the safe distribution of sodium oxybate, in connection with

FDA's approval of the generic sodium oxybate REMS or another oxybate REMS that may be submitted or approved in the future. Our settlement agreements with ANDA filers do not directly impact FDA's waiver of the single shared system REMS requirement, any other ANDA or NDA filer's ability to develop and implement the generic sodium oxybate REMS for its sodium oxybate product, or our ability to take any action with respect to the safety of the generic sodium oxybate REMS. We cannot predict the outcome or impact on our business of any future action that we may take with respect to FDA's waiver of the single shared system REMS requirement, its approval and tentative approval of generic versions of sodium oxybate or the consequences of distribution of sodium oxybate through the generic sodium oxybate REMS approved by FDA or another separate REMS.

REMS programs have increasingly drawn public scrutiny from the U.S. Congress, the Federal Trade Commission, or FTC, and FDA, with allegations that such programs are used as a means of improperly blocking or delaying competition. In December 2019, as part of the Further Consolidated Appropriations Act of 2020, the U.S. Congress passed legislation known as the Creating and Restoring Equal Access To Equivalent Samples Act, or CREATES. CREATES is intended to prevent companies from using REMS and other restricted distribution programs as a means to deny potential competitors access to product samples that are reasonably necessary to conduct testing in support of an application that references a listed drug or biologic, and provides such potential competitors a potential private right of action if the innovator fails to timely provide samples upon request. CREATES also grants FDA additional authority regarding approval of generic products with REMS.

It is possible that the FTC, FDA or other governmental authorities could claim that, or launch an investigation into whether, we are using our REMS programs in an anticompetitive manner or have engaged in other anticompetitive practices. The Federal Food, Drug and Cosmetic Act further states that a REMS ETASU shall not be used by an NDA holder to block or delay generic drugs or drugs covered by an application under Section 505(b)(2) from entering the market. In its 2015 letter approving the Xyrem REMS, FDA expressed concern that we were aware that the Xyrem REMS is blocking competition. From June 2020 to October 2021, we were served with a number of lawsuits that included allegations that we had used the Xyrem REMS to delay approval of generic sodium oxybate. In December 2020, these cases were centralized and transferred to the United States District Court for the Northern District of California, where the multidistrict litigation will proceed for the purpose of discovery and pre-trial proceedings. For additional information on these lawsuits, see Note 14, Commitments and Contingencies-Legal Proceedings of the Notes to Consolidated Financial Statements, included in Part IV of this Annual Report on Form 10-K. It is possible that additional lawsuits will be filed against us making similar or related allegations. We cannot predict the outcome of these or potential additional lawsuits; however, if the plaintiffs were to be successful in their claims, they may be entitled to injunctive relief or we may be required to pay significant monetary damages, which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

Pharmaceutical companies, including their agents and employees, are required to monitor adverse events occurring during the use of their products and report them to FDA. The patient counseling and monitoring requirements of the Xywav and Xyrem REMS provide more extensive information about adverse events experienced by patients taking Xywav and Xyrem, including deaths, than is generally available for other products that are not subject to similar REMS requirements. As required by FDA and other regulatory agencies, the adverse event information that we collect for Xywav and Xyrem is regularly reported to FDA and could result in FDA requiring changes to Xywav and/or Xyrem labeling, including additional warnings or additional boxed warnings, or requiring us to take other actions that could have an adverse effect on patient and prescriber acceptance of Xywav and Xyrem. As required by FDA, Xywav's and Xyrem's current labeling includes a boxed warning regarding the risk of central nervous system depression and misuse and abuse.

Any failure to demonstrate our substantial compliance with the REMS or any other applicable regulatory requirements to the satisfaction of FDA or another regulatory authority could result in such regulatory authorities taking actions in the future which could have a material adverse effect on oxybate product sales and therefore on our business, financial condition, results of operations and growth prospects.

Our inability to maintain or increase sales of Epidiolex/Epidyolex would have a material adverse effect on our business, financial condition, results of operations and growth prospects.

Our ability to maintain or increase sales of Epidiolex/Epidyolex (cannabidiol) is subject to many risks. While we have established our Epidiolex commercial team and have hired our U.S. and European sales forces, we will need to continue to maintain and further develop the teams in order to successfully coordinate the commercialization of Epidiolex. Even if we are successful in maintaining and continuing to develop our Epidiolex commercial team, there are many factors that could cause the commercialization of Epidiolex to be unsuccessful, including a number of factors that are outside our control. The commercial success of Epidiolex depends on the extent to which patients and physicians accept and adopt Epidiolex as a treatment for Lennox-Gastaut syndrome, or LGS, Dravet syndrome and Tuberous Sclerosis Complex, and we do not know whether our or others' estimates in this regard will be accurate. Physicians may not prescribe Epidiolex and patients may be unwilling to use Epidiolex if coverage is not provided or reimbursement is inadequate to cover a significant portion of the cost. Additionally,

any negative development for Epidiolex in the market, in clinical development for additional indications, or in regulatory processes in other jurisdictions, may adversely impact the commercial results and potential of Epidiolex.

While we expect our oxybate products and Epidiolex/Epidyolex to remain the largest parts of our business, our success also depends on our ability to effectively commercialize other products in our neuroscience and oncology therapeutic areas.

In addition to Xywav, Xyrem, Epidiolex/Epidyolex and our other neuroscience products and product candidates, we are commercializing a portfolio of products, including our other lead marketed products, Sunosi, Zepzelca, Rylaze, Vyxeos and Defitelio. An inability to effectively commercialize our other lead marketed products and to maximize their potential where possible through successful research and development activities, whether due to the evolving effects of the COVID-19 pandemic or otherwise, could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

Sunosi

We obtained approval of Sunosi® (solriamfetol) in the U.S. in 2019, in the European Union, or EU, in January 2020, in Canada in May 2021 and subsequently in other countries for the treatment of EDS associated with narcolepsy or OSA. Our ability to realize the anticipated benefits from our investment in Sunosi is subject to a number of risks and uncertainties, including the potential impacts of the continuing COVID-19 pandemic on the successful commercialization in the U.S. and the rolling launch in Europe; market acceptance of Sunosi; our ability, in a competitive retail pharmacy market, to differentiate Sunosi from other products that are prescribed to treat excessive sleepiness in patients with OSA or EDS in patients with narcolepsy; adequate coverage and reimbursement by government programs and other third party payors, including the impact of future coverage decisions by payors; restrictions on permitted promotional activities based on any additional limitations on the labeling for the product that may be required by FDA, or the European Commission, or the EC, or other regulatory authorities; and our ability to satisfy FDA's post-marketing requirements.

Zepzelca

Our ability to realize the anticipated benefits from our investment in Zepzelca® (lurbinectedin) is subject to a number of risks and uncertainties, including our ability to successfully commercialize Zepzelca in the U.S.; adequate supply of Zepzelca to meet demand; availability of favorable pricing and adequate coverage and reimbursement; the limited experience of, and need to educate, physicians in the use of Zepzelca for the treatment of metastatic small cell lung cancer, or SCLC; the potential for negative trial data read-outs in ongoing or future Zepzelca clinical trials; our and Pharma Mar, S.A., or PharmaMar's, ability to maintain accelerated approval or successfully complete a confirmatory study of Zepzelca; and the impact of the evolving effects of the COVID-19 pandemic on our ability to educate health care providers about Zepzelca in the treatment of relapsed, metastatic SCLC in the U.S. and on patients' access to lung cancer screening, diagnosis and treatment. If we are unable to successfully commercialize Zepzelca in the U.S. and Canada, or if sales of Zepzelca do not reach the levels we expect, our anticipated revenue from Zepzelca will be negatively affected, which would have an adverse effect on our business, financial condition, results of operations and growth prospects.

Rylaze

Our ability to realize the anticipated benefits from our investments in Rylaze™ (recombinant *Erwinia* asparaginase) is subject to a number of uncertainties, including our ability to successfully commercialize Rylaze in the U.S. including creating awareness among health care professionals and ensuring physicians are confident in its supply and that patients with acute lymphoblastic leukemia, or ALL, or lymphoblastic lymphoma, or LBL, will be given the appropriate course of therapy based on current FDA approval. In addition, there continues to be the potential of a competitive erwinia product being reintroduced into the marketplace that could create uncertainty in demand and utilization of Rylaze moving forward.

Vyxeos

Our ability to realize the anticipated benefits from our investment in Vyxeos® (daunorubicin and cytarabine) liposome for injection by successfully and sustainably growing sales is subject to a number of risks and uncertainties, including our ability to differentiate Vyxeos from other liposomal chemotherapies and generically available chemotherapy combinations with which physicians and treatment centers are more familiar; acceptance by hospital pharmacy and therapeutics committees in the U.S., the EU and other countries; the increasing complexity of the acute myeloid leukemia, or AML, landscape requiring changes in patient identification and treatment selection, including diagnostic tests and monitoring that clinicians may find challenging to incorporate; the use of new and novel compounds in AML that are either used off-label or are only approved for use in combination with other agents and that have not been tested in combination with Vyxeos; the increasing use of venetoclax, which received full FDA approval in October 2020 for AML treatment; the limited size of the population of high-risk AML patients who may potentially be indicated for treatment with Vyxeos, particularly as a result of the shift of healthcare resources toward less intensive outpatient AML treatments in the U.S. in light of the COVID-19 pandemic which is directly negatively impacting, or delaying, the use of Vyxeos, as well as the suspension of in-person interactions with healthcare professionals due to the COVID-19 pandemic; the availability of adequate coverage, pricing and reimbursement approvals; and competition from

new and existing products and potential competition from products in development. Although we saw some recovery in demand for Vyxeos beginning in the end of the second quarter of 2020, due to the ongoing impacts of the COVID-19 pandemic, we continue to expect a negative impact on demand growth trends for and utilization of Vyxeos compared to historical periods. If sales of Vyxeos do not reach the levels we expect, our anticipated revenue from the product would be negatively affected, which would have an adverse effect on our business, financial condition, results of operations and growth prospects.

Defitelio

Our ability to maintain and grow sales and to realize the anticipated benefits from our investment in Defitelio® (defibrotide sodium) is subject to a number of risks and uncertainties, including continued acceptance by hospital pharmacy and therapeutics committees in the U.S., the EU and other countries; the continued availability of favorable pricing and adequate coverage and reimbursement; the limited experience of, and need to educate, physicians in recognizing, diagnosing and treating hepatic veno-occlusive disease, or VOD, particularly in adults; the possibility that physicians recognizing VOD symptoms may not initiate or may delay initiation of treatment while waiting for those symptoms to improve, or may terminate treatment before the end of the recommended dosing schedule; and the limited size of the population of VOD patients who are indicated for treatment with Defitelio (particularly if changes in hematopoietic stem cell transplantation treatment protocols reduce the incidence of VOD diagnosis and demand for Defitelio).

Although we saw a resurgence in demand for Defitelio in the U.S. and outside the U.S. beginning in the end of the second quarter of 2020, due to the evolving effects of the COVID-19 pandemic, the reprioritization of healthcare resources and related delays, postponements or suspensions of certain medical procedures such as stem cell transplants, we continue to expect a negative impact on demand growth trends and utilization of Defitelio compared to historical periods. If sales of Defitelio do not reach the levels we expect, our anticipated revenue from the product would be negatively affected and our business, financial condition, results of operations and growth prospects would be adversely affected. In addition, because VOD is an ultra-rare disease, we have experienced inter-quarter variability in our Defitelio sales, which makes Defitelio sales difficult to predict from period to period. As a result, Defitelio sales results or trends in any period may not necessarily be indicative of future performance.

We face substantial competition from other companies, including companies with larger sales organizations and more experience working with large and diverse product portfolios, and face competition from generic drugs and potentially from non-FDA approved cannabidiol preparations.

Our products compete, and our product candidates may in the future compete, with currently existing therapies, including generic drugs, product candidates currently under development by us and others and/or future product candidates, including new chemical entities that may be safer or more effective or more convenient than our products. Any products that we develop may be commercialized in competitive markets, and our competitors, which include large global pharmaceutical companies and small research-based companies and institutions, may succeed in developing products that render our products obsolete or noncompetitive. Many of our competitors, particularly large pharmaceutical and life sciences companies, have substantially greater financial, operational and human resources than we do. Smaller or earlier stage companies may also prove to be significant competitors, particularly through focused development programs and collaborative arrangements with large, established companies. In addition, many of our competitors deploy more personnel to market and sell their products than we do, and we compete with other companies to recruit, hire, train and retain pharmaceutical sales and marketing personnel. If our sales force and sales support organization are not appropriately resourced and sized to adequately promote our products, the commercial potential of our current and any future products may be diminished. In any event, the commercial potential of our current products and any future products may be reduced or eliminated if our competitors develop or acquire and commercialize generic or branded products that are safer or more effective, are more convenient or are less expensive than our products. If we are unable to compete successfully, our commercial opportunities will be reduced and our business, results of operations and financial conditions may be materially harmed.

There is a substantial amount of change occurring in the U.S. regarding the use of medical and recreational marijuana products. While federal law prohibits the sale and distribution of most marijuana products not approved or authorized by FDA, 46 states and the District of Columbia have legalized either cannabidiol, or CBD, or marijuana for either recreational or medical use, or both. Under the U.S. Farm Bill, enacted in late 2018, certain extracts and other material derived from cannabis are no longer controlled under the Federal Controlled Substances Act, or CSA. Although the marketing of such products as a food, dietary supplement, or for medical purposes remains subject to FDA requirements, FDA continues to evaluate regulatory pathways to permit CBD in conventional foods and dietary supplements. In addition, Congressional efforts related to legalization of marijuana continue. Although our business is distinct from that of entities marketing FDA-unapproved marijuana and CBD-containing dietary supplement, future legislation or federal government action authorizing the sale, distribution, use, and insurance reimbursement of non-FDA approved marijuana or cannabinoid products could increase competition for and adversely affect our ability to generate sales of Epidiolex and our cannabinoid product candidates.

In addition, Epidiolex and nabiximols compete with product offerings from a variety of companies. FDA approved Zogenix, Inc.'s low-dose fenfluramine, or Fintepla, in Dravet syndrome in June 2020, and Zogenix submitted its supplemental NDA for LGS in 2021. In January 2022, Zogenix announced that it entered into a definitive agreement with UCB for the acquisition of Zogenix by UCB. Ovid Therapeutics Inc./Takeda Pharmaceutical Company Limited, Eisai Company Limited, and Marinus Pharmaceuticals, Inc. are developing therapies for treating Developmental and Epileptic Encephalopathies (includes Dravet and LGS). Stiripentol has been approved in Europe for several years to treat Dravet syndrome and was approved in 2018 by FDA. Zynerba Pharmaceuticals, Inc. is developing a topical formulation of CBD, for which it is working with FDA on a path forward on CONNECT-FX data for Zygel in Fragile X syndrome. There are a number of public and private companies in the early stages of developing genetic therapies for the underlying causes of Dravet syndrome, including Stoke Therapeutics, Inc., which has an antisense oligonucleotide, STK-001, in early clinical trials. Other companies, including those with greater resources than us may announce similar plans in the future. In addition, there are non-FDA approved CBD preparations being made available from companies in the medical marijuana industry, which might attempt to compete with Epidiolex and, if approved by FDA, nabiximols. If we are unable to compete successfully, our commercial opportunities will be reduced and our business, results of operations and financial conditions may be materially harmed.

For a description of the competition that our lead marketed products and most advanced product candidates face or may face, see the discussion in "Business—Competition" in Part I, Item 1 of this Annual Report on Form 10-K and the risk factor under the heading "*The introduction of new products in the U.S. market that compete with, or otherwise disrupt the market for, our oxybate products and product candidates would adversely affect sales of our oxybate products and product candidates*" in this Part I, Item 1A.

Adequate coverage and reimbursement from third party payors may not be available for our products and we may be unable to successfully contract for coverage from pharmacy benefit managers and other organizations; conversely, to secure coverage from these organizations, we may be required to pay rebates or other discounts or other restrictions to reimbursement, either of which could diminish our sales or adversely affect our ability to sell our products profitably.

In both U.S. and non-U.S. markets, our ability to successfully commercialize and achieve market acceptance of our products depends in significant part on adequate financial coverage and reimbursement from third party payors, including governmental payors (such as the Medicare and Medicaid programs in the U.S.), managed care organizations and private health insurers. Without third party payor reimbursement, patients may not be able to obtain or afford prescribed medications. In addition, reimbursement guidelines and incentives provided to prescribing physicians by third party payors may have a significant impact on the prescribing physicians' willingness and ability to prescribe our products. The demand for, and the profitability of, our products could be materially harmed if state Medicaid programs, the Medicare program, other healthcare programs in the U.S. or elsewhere, or third party commercial payors in the U.S. or elsewhere deny reimbursement for our products, limit the indications for which our products will be reimbursed, or provide reimbursement only on unfavorable terms. In particular, we cannot predict to what extent the evolving effects of the COVID-19 pandemic may disrupt global healthcare systems and access to our products or result in a widespread loss of individual health insurance coverage due to unemployment, a shift from commercial payor coverage to government payor coverage, or an increase in demand for patient assistance and/or free drug programs, any of which could adversely affect net revenue.

As part of the overall trend toward cost containment, third party payors often require prior authorization for, and require reauthorization for continuation of, prescription products or impose step edits, which require prior use of another medication, usually a generic or preferred brand, prior to approving coverage for a new or more expensive product. Such restrictive conditions for reimbursement and an increase in reimbursement-related activities can extend the time required to fill prescriptions and may discourage patients from seeking treatment. We cannot predict actions that third party payors may take, or whether they will limit the access and level of reimbursement for our products or refuse to provide any approvals or coverage. From time to time, third party payors have refused to provide reimbursement for our products, and others may do so in the future.

Third party payors increasingly examine the cost-effectiveness of pharmaceutical products, in addition to their safety and efficacy, when making coverage and reimbursement decisions. We may need to conduct expensive pharmacoeconomic and/or clinical studies in order to demonstrate the cost-effectiveness of our products. If our competitors offer their products at prices that provide purportedly lower treatment costs than our products, or otherwise suggest that their products are safer, more effective or more cost-effective than our products, this may result in a greater level of access for their products relative to our products, which would reduce our sales and harm our results of operations. In some cases, for example, third party payors try to encourage the use of less expensive generic products through their prescription benefit coverage and reimbursement and co-pay policies. Because some of our products compete in a market with both branded and generic products, obtaining and maintaining access and reimbursement coverage for our products may be more challenging than for products that are new chemical entities for which no therapeutic alternatives exist.

Third party pharmacy benefit managers, or PBMs, other similar organizations and payors can limit coverage to specific products on an approved list, or formulary, which might not include all of the approved products for a particular indication, and

to exclude drugs from their formularies in favor of competitor drugs or alternative treatments, or place drugs on formulary tiers with higher patient co-pay obligations, and/or to mandate stricter utilization criteria. Formulary exclusion effectively encourages patients and providers to seek alternative treatments, make a complex and time-intensive request for medical exemptions, or pay 100% of the cost of a drug. In addition, in many instances, certain PBMs, other similar organizations and third party payors may exert negotiating leverage by requiring incremental rebates, discounts or other concessions from manufacturers in order to maintain formulary positions, which could continue to result in higher gross to net deductions for affected products. In this regard, we have entered into agreements with PBMs and payor accounts to provide rebates to those entities related to formulary coverage for our products, but we cannot guarantee that we will be able to agree to coverage terms with other PBMs and other third party payors. Payors could decide to exclude our products from formulary coverage lists, impose step edits that require patients to try alternative, including generic, treatments before authorizing payment for our products, limit the types of diagnoses for which coverage will be provided or impose a moratorium on coverage for products while the payor makes a coverage decision. An inability to maintain adequate formulary positions could increase patient cost-sharing for our products and cause some patients to determine not to use our products. Any delays or unforeseen difficulties in reimbursement approvals could limit patient access, depress therapy adherence rates, and adversely impact our ability to successfully commercialize our products. If we are unsuccessful in maintaining broad coverage for our products, our anticipated revenue from and growth prospects for our products could be negatively affected.

In many countries outside the U.S., procedures to obtain price approvals, coverage and reimbursement can take considerable time after the receipt of marketing authorization. Many European countries periodically review their reimbursement of medicinal products, which could have an adverse impact on reimbursement status. In addition, we expect that legislators, policymakers and healthcare insurance funds in the EU member states will continue to propose and implement cost-containing measures, such as lower maximum prices, lower or lack of reimbursement coverage and incentives to use cheaper, usually generic, products as an alternative to branded products, and/or branded products available through parallel import to keep healthcare costs down. Moreover, in order to obtain reimbursement for our products in some European countries, including some EU member states, we may be required to compile additional data comparing the cost-effectiveness of our products to other available therapies. Health Technology Assessment, or HTA, of medicinal products is becoming an increasingly common part of the pricing and reimbursement procedures in some EU member states, including those representing the larger markets. The HTA process, which is currently governed by national laws in each EU member state, is the procedure to assess therapeutic, economic and societal impact of a given medicinal product in the national healthcare systems of the individual country. The outcome of an HTA will often influence the pricing and reimbursement status granted to these medicinal products by the competent authorities of individual EU member states. The extent to which pricing and reimbursement decisions are influenced by the HTA of the specific medicinal product currently varies between EU member states, although beginning in January 2025, the EU HTA regulation will apply; this regulation aims to harmonize the clinical benefit assessment of HTA across the EU. If we are unable to maintain favorable pricing and reimbursement status in EU member states that represent significant markets, our anticipated revenue from and growth prospects for our products in the EU could be negatively affected. For example, the EC granted marketing authorization for Vyxeos in August 2018, for Epidyolex in September 2019 and for Sunosi in January 2020, and, as part of our rolling launches of Vyxeos, Epidyolex and Sunosi in Europe, we are making pricing and reimbursement submissions in European countries. Due to the evolving effects of the COVID-19 pandemic, we currently anticipate delays by certain European regulatory authorities in their pricing and reimbursement reviews. If we experience setbacks or unforeseen difficulties in obtaining favorable pricing and reimbursement decisions, including as a result of regulatory review delays due to the COVID-19 pandemic, planned launches in the affected EU member states would be delayed, which could negatively impact anticipated revenue from and growth prospects for Vyxeos, Epidyolex and/or Sunosi.

The pricing of pharmaceutical products has come under increasing scrutiny as part of a global trend toward healthcare cost containment and resulting changes in healthcare law and policy may impact our business in ways that we cannot currently predict, which could have a material adverse effect on our business and financial condition.

Political, economic and regulatory influences are subjecting the healthcare industry in the U.S. to fundamental changes, particularly given the current atmosphere of mounting criticism of prescription drug costs in the U.S. We expect there will continue to be legislative and regulatory proposals to change the healthcare system in ways that could impact our ability to sell our products profitably, as governmental oversight and scrutiny of biopharmaceutical companies is increasing. For example, we anticipate that the U.S. Congress, state legislatures, and federal and state regulators may adopt or accelerate adoption of new healthcare policies and reforms intended to curb healthcare costs, such as federal and state controls on reimbursement for drugs (including under Medicare, Medicaid and commercial health plans), new or increased requirements to pay prescription drug rebates and penalties to government health care programs, and additional pharmaceutical cost transparency policies that aim to require drug companies to justify their prices through required disclosures.

Legislative and regulatory proposals that have recently been considered include, among other things, proposals to limit the terms of patent litigation settlements with generic sponsors, to define certain conduct around patenting and new product development as unfair competition, to facilitate the importation of drugs into the U.S. from other countries, and to increase

manufacturer liability in the Medicare Part D pharmaceutical benefit. Legislative and regulatory proposals to reform the regulation of the pharmaceutical industry and reimbursement for pharmaceutical drugs are continually changing, and all such considerations may adversely affect our business and industry in ways that we cannot accurately predict.

There is also ongoing activity related to health care coverage. The Affordable Care Act substantially changed the way healthcare is financed by both governmental and private insurers. These changes impacted previously existing government healthcare programs and have resulted in the development of new programs, including Medicare payment-for-performance initiatives. Further, the Biden administration and U.S. Congress have taken and are expected to continue to take notable steps towards expanding health care coverage beyond the Affordable Care Act, which could have ramifications for the pharmaceutical industry. Additional legislative changes, regulatory changes, or guidance could be adopted, which may impact the marketing approvals and reimbursement for our product candidates. For example, there has been increasing legislative, regulatory, and enforcement interest in the U.S. with respect to drug pricing practices. There have been several Congressional inquiries and proposed and enacted federal and state legislation and regulatory initiatives designed to, among other things, bring more transparency to product pricing, evaluate the relationship between pricing and manufacturer patient programs, and reform government healthcare program reimbursement methodologies for drug products.

If healthcare policies or reforms intended to curb healthcare costs are adopted or if we experience negative publicity with respect to pricing of our products or the pricing of pharmaceutical drugs generally, the prices that we charge for our products may be affected, our commercial opportunity may be limited and/or our revenues from sales of our products may be negatively impacted. We have periodically increased the price of Xyrem, most recently in January 2022, and there is no guarantee that we will make similar price adjustments to Xywav and Xyrem in the future or that price adjustments we have taken or may take in the future will not negatively affect Xywav or Xyrem sales volumes and revenues. We also have made and may in the future make price adjustments on our other products. There is no guarantee that such price adjustments will not negatively affect our reputation and our ability to secure and maintain reimbursement coverage for our products, which could limit the prices that we charge for our products, including Xywav and Xyrem, limit the commercial opportunities for our products and/or negatively impact revenues from sales of our products.

If we become the subject of any future government investigation or U.S. Congressional oversight with respect to drug pricing or other business practices, we could incur significant expense and could be distracted from operation of our business and execution of our strategy. Any such investigation or hearing could also result in reduced market acceptance and demand for our products, could harm our reputation and our ability to market our products in the future, and could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

We expect that legislators, policymakers and healthcare insurance funds in Europe will continue to propose and implement cost-containing measures to keep healthcare costs down; particularly due to the financial strain that the COVID-19 pandemic has placed on their healthcare systems. These measures could include limitations on the prices we will be able to charge for our products or the level of reimbursement available for these products from governmental authorities or third party payors. Further, an increasing number of European and other foreign countries use prices for medicinal products established in other countries as “reference prices” to help determine the price of the product in their own territory. Consequently, a downward trend in prices of medicinal products in some countries could contribute to similar downward trends elsewhere.

In addition to access, coverage and reimbursement, the commercial success of our products depends upon their market acceptance by physicians, patients, third party payors and the medical community.

If physicians do not prescribe our products, we cannot generate the revenues we anticipate from product sales. Market acceptance of each of our products by physicians, patients, third party payors and the medical community depends on:

- the clinical indications for which a product is approved and any restrictions placed upon the product in connection with its approval, such as a REMS or equivalent obligation imposed in a European or other foreign country, patient registry requirements or labeling restrictions;
- the prevalence of the disease or condition for which the product is approved and its diagnosis;
- the efficacy of the product in regular use;
- the severity of side effects and other risks in relation to the benefits of our products;
- unanticipated serious adverse events;
- acceptance by physicians and patients of each product as a safe and effective treatment;
- availability of sufficient product inventory to meet demand;
- physicians’ decisions relating to treatment practices based on availability of product;
- perceived clinical superiority and/or advantages over alternative treatments;

- overcoming negative publicity surrounding illicit use of
    - GHB or
    - cannabinoid and marijuana products

  and the view of patients, law enforcement agencies, physicians and regulators of our products as being the same or similar to illicit products;
- relative convenience and ease of administration;
- with respect to Xywav and Xyrem, physician and patient assessment of the burdens associated with obtaining or maintaining the certifications required under the Xywav and Xyrem REMS;
- the cost of treatment in relation to alternative treatments, including generic products; and
- the availability of financial or other assistance for patients who are uninsured or underinsured.

Because of our dependence upon market acceptance of our products, any adverse publicity associated with harm to patients or other adverse events resulting from the use or misuse of any of our products or any similar products distributed by other companies, including generic versions of our products, could materially and adversely affect our business, financial condition, results of operations and growth prospects.

Delays or problems in the supply of our products for sale or for use in clinical trials, loss of our single source suppliers or failure to comply with manufacturing regulations could materially and adversely affect our business, financial condition, results of operations and growth prospects.

The manufacture of pharmaceutical products requires significant expertise and capital investment, including the development of process controls required to consistently produce the API and the finished product in sufficient quantities while meeting detailed product specifications on a repeated basis. We and our suppliers may encounter difficulties in production, including difficulties with the supply of manufacturing materials, production costs and yields, process controls, quality control and quality assurance, including testing of stability, impurities and impurity levels and other product specifications by validated test methods, and compliance with strictly enforced U.S., state and non-U.S. regulations. In addition, we and our suppliers are subject to FDA's current Good Manufacturing Practices, or cGMP, requirements, DEA regulations and equivalent rules and regulations prescribed by non-U.S. regulatory authorities. If we or any of our suppliers encounter manufacturing, quality or compliance difficulties with respect to any of our products, whether due to the evolving effects of the COVID-19 pandemic (including as a result of disruptions of global shipping and the transport of products) or otherwise, we may be unable to obtain or maintain regulatory approval or meet commercial demand for such products, which could adversely affect our business, financial condition, results of operations and growth prospects. In addition, we could be subject to enforcement action by regulatory authorities for our failure to comply with cGMP with respect to the products we manufacture in our facilities as well as for our failure to adequately oversee compliance with cGMP by any of our third party suppliers operating under contract. Moreover, failure to comply with applicable legal and regulatory requirements subjects us and our suppliers to possible regulatory action, including restrictions on supply or shutdown, which may adversely affect our or a supplier's ability to supply the ingredients or finished products we need.

We have a manufacturing and development facility in Athlone, Ireland where we manufacture Xywav and Xyrem, a manufacturing plant in Villa Guardia, Italy where we produce the defibrotide drug substance and a manufacturing and development facility in the U.K. at Kent Science Park, where we produce Epidiolex/Epidyolex and Sativex. We currently do not have our own commercial manufacturing or packaging capability for our other products, product candidates or their APIs. As a result, our ability to develop and supply products in a timely and competitive manner depends primarily on third party suppliers being able to meet our ongoing commercial and clinical trial needs for API, other raw materials, packaging materials and finished products.

In part due to the limited market size for our products and product candidates, we have a single source of supply for most of our marketed products, product candidates and their APIs. Single sourcing puts us at risk of interruption in supply in the event of manufacturing, quality or compliance difficulties. If one of our suppliers fails or refuses to supply us for any reason, it would take a significant amount of time and expense to implement and execute the necessary technology transfer to, and to qualify, a new supplier. FDA and similar international or national regulatory bodies must approve manufacturers of the active and inactive pharmaceutical ingredients and certain packaging materials used in our products. If there are delays in qualifying new suppliers or facilities or a new supplier is unable to meet FDA's or similar international regulatory body's requirements for approval, there could be a shortage of the affected products for the marketplace or for use in clinical studies, or both, which could negatively impact our anticipated revenues and could potentially cause us to breach contractual obligations with customers or to violate local laws requiring us to deliver the product to those in need.

We are responsible for the manufacture and supply of Sativex (nabiximols) to our collaboration partners and for the manufacture and supply of Epidiolex/Epidyolex, nabiximols and other cannabinoid product candidates for commercial use and for use in clinical trials. The manufacturing of Epidiolex/Epidyolex, nabiximols and our product candidates necessitates compliance with GMP and other regulatory requirements in jurisdictions internationally. Our ability to successfully manufacture Epidiolex/Epidyolex, nabiximols and other cannabinoid product candidates involves cultivation of botanical raw material from specific cannabinoid plants, extraction and purification processes, manufacture of finished products and labeling and packaging, which includes product information, tamper evidence and anti-counterfeit features, under tightly controlled processes and procedures. In addition, we must ensure chemical consistency among our batches, including clinical batches and, if approved, marketing batches. Demonstrating such consistency may require typical manufacturing controls as well as clinical data. We must also ensure that our batches conform to complex release specifications. For certain steps in the manufacturing process for nabiximols, we are currently reliant on single manufacturing facilities and no back-up facilities are yet in place. We have a second site at which we can grow the specific cannabinoid plants that produce the CBD used in Epidiolex/Epidyolex, a second site at which we can extract CBD from botanical raw material and a second site at which we can crystallize the purified CBD from the liquid plant extract. Because nabiximols is a complex mixture manufactured from plant materials, and because the release specifications may not be identical in all countries, certain batches may fail release testing and not be able to be commercialized. A number of our product candidates (excluding Epidiolex/Epidyolex) also consist of a complex mixture manufactured from plant materials, and are therefore subject to a similar risk. If we are unable to manufacture Epidiolex/Epidyolex, nabiximols or other product candidates in accordance with regulatory specifications, including Good Manufacturing Practice, or GMP, or if there are disruptions in our manufacturing process due to damage, loss or otherwise, or failure to pass regulatory inspections of our manufacturing facilities, we may not be able to meet current demand or supply sufficient product for use in clinical trials, and this may also harm our ability to commercialize Epidiolex/Epidyolex, nabiximols and our product candidates on a timely or cost-competitive basis, if at all. Our manufacturing program requires significant time and resources and may not be successful, may lead to delays, interruptions to supply or may prove to be more costly than anticipated.

Vyxeos is manufactured by Baxter Oncology GmbH, or Baxter, which is a sole source supplier from a single site location. There have been batch failures due to mechanical, component, raw materials and other issues in the production of Vyxeos, and batches have been produced that have otherwise not been in compliance with applicable specifications. We are continuing to work with Baxter and others to address manufacturing complexities related to Vyxeos. Moreover, the proprietary technology that supports the manufacture of Vyxeos is not easily transferable. Consequently, engaging an alternate manufacturer may be difficult, costly and time-consuming. If we fail to obtain a sufficient supply of Vyxeos in accordance with applicable specifications on a timely basis, our sales of Vyxeos, our future maintenance and potential growth of the market for this product, our ability to conduct ongoing and future clinical trials of Vyxeos, and our business, financial condition, results of operations and growth prospects could be materially adversely affected. In addition, while the APIs in Vyxeos, daunorubicin and cytarabine, are available from a number of suppliers, certain suppliers have received warning letters from FDA. As a result, we have qualified other suppliers for each API, and we provided the qualification data to FDA. If FDA restricts importation of API from either supplier, and we are unable to qualify API from additional suppliers in a timely manner, or at all, our ability to successfully commercialize Vyxeos and generate sales of this product at the level we expect and to conduct ongoing and future clinical trials of Vyxeos could be materially and adversely affected.

Rylaze drug substance is manufactured by AGC Biologics at its facility in Copenhagen, Denmark and the drug product is manufactured and packaged by Patheon at its facility in Greenville, North Carolina. Both sites have ample capacity to support forecast demand and we have secured supply for more than one year's forecast demand. To successfully manufacture Rylaze, the manufacturer must have an adequate master and working cell bank. If we fail to obtain a sufficient supply of Rylaze in accordance with applicable specifications on a timely basis, our sales of Rylaze, our future maintenance and potential growth of the market for this product, our competitive advantage over competing products that have supply constraints, and our business, financial condition, results of operations and growth prospects could be materially adversely affected.

In addition, in order to conduct our ongoing and any future clinical trials of, complete marketing authorization submissions for, and potentially launch our other product candidates, we also need to have sufficient quantities of product manufactured.

Moreover, to obtain approval from FDA or a similar international or national regulatory body of any product candidate, we or our suppliers for that product must obtain approval by the applicable regulatory body to manufacture and supply product, in some cases based on qualification data provided to the applicable body as part of our regulatory submission. Any delay in generating, or failure to generate, data required in connection with submission of the chemistry, manufacturing and controls portions of any regulatory submission could negatively impact our ability to meet our anticipated submission dates, and therefore our anticipated timing for obtaining FDA or similar international or national regulatory body approval, or our ability to obtain regulatory approval at all. In addition, any failure of us or a supplier to obtain approval by the applicable regulatory body to manufacture and supply product or any delay in receiving, or failure to receive, adequate supplies of a product on a timely basis or in accordance with applicable specifications could negatively impact our ability to successfully launch and commercialize products and generate sales of products at the levels we expect.

If the effects of the COVID-19 pandemic become more severe and begin to impact supply of manufacturing materials or essential distribution systems such as general delivery services, or require us or our suppliers to again cease or restrict operations at our respective manufacturing facilities, we could experience disruptions to our supply chain and operations, and associated delays in the manufacturing and supply of our products, which would adversely impact our ability to generate sales of our approved products and our business, financial condition, results of operations and growth prospects would be materially adversely affected. For example, supply chain interruptions and shortage of construction materials could lead to delays and rising costs associated with our planned construction project at our commercial manufacturing facility in the U.K. at Kent Science Park. In addition, energy prices have spiked recently due to global macro-economic issues, which can have a direct impact on CO2 prices and availability. CO2 is a critical raw material for manufacturing our cannabinoid products.

Risks Related to Growth of Our Product Portfolio and Research and Development

Our future success depends on our ability to successfully develop and obtain and maintain regulatory approvals for our late-stage product candidates and, if approved, to successfully launch and commercialize those product candidates.

The testing, manufacturing and marketing of our products require regulatory approvals, including approval from FDA and similar bodies in Europe and other countries. If FDA, the European Medicines Agency, or EMA, or the competent authorities of the EU member states or other European countries determine that our quality, safety or efficacy data do not warrant marketing approval for a product candidate, we could be required to conduct additional clinical trials as a condition to receiving approval, which could be costly and time-consuming and could delay or preclude the approval of our application. Our inability to obtain and maintain regulatory approval for our product candidates in the U.S. and internationally and to successfully commercialize new products that are approved would prevent us from receiving a return on our investments and could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

Due to the evolving effects of the COVID-19 pandemic, it is possible that we could experience delays in the timing of marketing application review by regulatory authorities and/or our interactions with regulatory authorities due to limited staffing or working hours of governmental employees, governmental “stay-at-home” orders and travel restrictions with respect to physical inspections if required for regulatory approval, or the diversion of regulatory authority efforts and attention to approval of other therapeutics or other activities related to COVID-19, which could delay anticipated approval decisions and otherwise delay or limit our ability to make planned regulatory submissions or obtain new product approvals. For example, due to travel restrictions in 2021 that prevented an on-site inspection, we experienced a delay in FDA’s approval of GP Pharm as a second manufacturer of Zepzelca. It is possible that we could experience delays in regulatory interactions and review of submissions due to COVID-19 impacts described above, such as with respect to our development pathway for nabiximols.

Even if we receive approval of a product, regulatory authorities may impose significant labeling restrictions or requirements, including limitations on the dosing of the product, requirements around the naming or strength of a product, restrictions on indicated uses for which we may market the product, the imposition of a boxed warning or other warnings and precautions, and/or the requirement for a REMS or equivalent obligation imposed in a European or other foreign country to ensure that the benefits of the drug outweigh the risks. FDA requires a REMS and a boxed warning for Xywav and Xyrem, and similar restrictions could be imposed on other products in the future. Our receipt of approval for narrower indications than sought, restrictions on marketing through a REMS or equivalent obligation imposed in a European or other foreign country, or significant labeling restrictions or requirements in an approved label such as a boxed warning, could have a negative impact on our ability to recoup our research and development costs and to successfully commercialize that product, any of which could materially and adversely affect our business, financial condition, results of operations and growth prospects.

Regulatory authorities may also impose post-marketing obligations as part of their approval, which may lead to additional costs and burdens associated with commercialization of the drug, and may pose a risk to maintaining approval of the drug. We are subject to certain post-marketing requirements and commitments in connection with the approval of certain of our products, including Epidiolex, Defitelio, Vyxeos, Sunosi, Rylaze and Zepzelca. These post-marketing requirements and commitments include satisfactorily conducting multiple post-marketing clinical trials and safety studies. For example, FDA granted accelerated approval to Zepzelca for relapsed SCLC based on data from a Phase 2 trial, which approval is contingent upon verification and description of clinical benefit in a post-marketing clinical trial. We and our licensor PharmaMar are committed to the further study of lurbinectedin, both as a single agent and in combination, and have reached agreement with FDA regarding a confirmatory clinical development program. Our failure to confirm its clinical benefit could result in the withdrawal of approval of Zepzelca, which could have a material adverse effect on our business, financial condition, results of operations and growth prospects. With respect to FDA’s and EC’s approvals of Epidiolex/Epidyolex, we are subject to certain post-marketing requirements. Failure to comply with these post-marketing requirements could result in withdrawal of our marketing approvals for Epidiolex/Epidyolex and/or other civil or criminal penalties. In any event, if we are unable to comply with our post-marketing obligations imposed as part of the marketing approvals in the U.S., the EU, or other countries, our

approval may be varied, suspended or revoked, product supply may be delayed and our sales of our products could be materially adversely affected.

We are pursuing activities related to the development of additional asparaginase products for patients with ALL or other hematological malignancies. Several of our external research and development collaborations are focused on these efforts, including our agreement with Ligand Pharmaceuticals Incorporated, or Ligand. We developed Rylaze, a recombinant Erwinia asparaginase product for the treatment of patients with ALL and LBL who have hypersensitivity to E. coli-derived asparaginase, under our Ligand agreement. We also have clinical development efforts in a variety of other areas, including those focused on expanding the potential of Defitelio, Epidiolex/Epidyolex, Vyxeos, Sunosi, Rylaze and Xywav, as well as clinical development efforts focused on suvecaltamide (JZP385) for the treatment of essential tremor, JZP150 for post-traumatic stress disorder and nabiximols for multiple sclerosis-related spasticity. Because combination regimens and the continual generation of new data have become particularly important in AML, if we are unable to initiate multiple combination studies, safely combine Vyxeos with novel agents, or if efficacy results do not meet clinicians' expectations, our growth prospects could be materially adversely affected. Epidiolex has been administered only to a limited number of patients and in limited populations in clinical trials. While FDA and EC granted approval of Epidiolex/Epidyolex based on the data included in GW's NDA, sNDA and marketing authorization application, we do not know whether the results will be consistent with those resulting from administration of the drug to a large number of patients. New data relating to Epidiolex/Epidyolex, including from adverse event reports and post-marketing studies in the U.S. and Europe, and from other ongoing clinical trials, may result in changes to the product label and/or imposition of a REMS and may adversely affect sales, or result in withdrawal of Epidiolex/Epidyolex from the market. FDA, EMA and regulatory authorities in other jurisdictions may also consider the new data in reviewing Epidiolex/Epidyolex marketing applications for indications other than our approved uses in other jurisdictions, or impose additional post-approval requirements. If any of these actions were to occur, it could result in significant expense and delay or limit our ability to generate sales of Epidiolex/Epidyolex. If we are not successful in the clinical development of our product candidates, if we are unable to obtain regulatory approval for our product candidates in a timely manner, or at all, or if sales of an approved product do not reach the levels we expect, our anticipated revenue from our product candidates would be negatively affected, which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

We may not be able to successfully identify and acquire or in-license additional products or product candidates to grow our business, and, even if we are able to do so, we may otherwise fail to realize the anticipated benefits of these transactions.

In addition to continued investment in our research and development pipeline, we intend to grow our business by acquiring or in-licensing, and developing, including with collaboration partners, additional products and product candidates that we believe are highly differentiated and have significant commercial potential. However, we may be unable to identify or consummate suitable acquisition or in-licensing opportunities, and this inability could impair our ability to grow our business. Other companies, many of which may have substantially greater financial, sales and marketing resources, compete with us for these opportunities. Even if appropriate opportunities are available, we may not be able to successfully identify them, or we may not have the financial resources necessary to pursue them.

Even if we are able to successfully identify and acquire, in-license or develop additional products or product candidates, we may not be able to successfully manage the risks associated with integrating any products or product candidates into our portfolio or the risks arising from anticipated and unanticipated problems in connection with an acquisition or in-licensing. Further, while we seek to mitigate risks and liabilities of potential acquisitions and in-licensing transactions through, among other things, due diligence, there may be risks and liabilities that such due diligence efforts fail to discover, that are not disclosed to us, or that we inadequately assess. Any failure in identifying and managing these risks, liabilities and uncertainties effectively, could have a material adverse effect on our business, results of operations and financial condition. In addition, product and product candidate acquisitions, particularly when the acquisition takes the form of a merger or other business consolidation such as our acquisition of GW, have required, and any similar future transactions also will require, significant efforts and expenditures, including with respect to transition and integration activities. We may encounter unexpected difficulties, or incur substantial costs, in connection with potential acquisitions and similar transactions, which include:

- the need to incur substantial debt and/or engage in dilutive issuances of equity securities to pay for acquisitions;
- the potential disruption of our historical core business;
- the strain on, and need to continue to expand, our existing operational, technical, financial and administrative infrastructure;
- the difficulties in integrating acquired products and product candidates into our portfolio;
- the difficulties in assimilating employees and corporate cultures;
- the failure to retain key managers and other personnel;

- the need to write down assets or recognize impairment charges;
- the diversion of our management's attention to integration of operations and corporate and administrative infrastructures; and
- any unanticipated liabilities for activities of or related to the acquired business or its operations, products or product candidates.

As a result of these or other factors, products or product candidates we acquire, or obtain licenses to, may not produce the revenues, earnings or business synergies that we anticipated, acquired or in-licensed product candidates may not result in regulatory approvals, and acquired or licensed products may not perform as expected. Failure to manage effectively our growth through acquisitions or in-licensing transactions could adversely affect our growth prospects, business, results of operations and financial condition.

Conducting clinical trials is costly and time-consuming, and the outcomes are uncertain. A failure to prove that our product candidates are safe and effective in clinical trials, or to generate data in clinical trials to support expansion of the therapeutic uses for our existing products, could materially and adversely affect our business, financial condition, results of operations and growth prospects.

As a condition to regulatory approval, each product candidate must undergo extensive and expensive preclinical studies and clinical trials to demonstrate that the product candidate is safe and effective. The results at any stage of the development process may lack the desired safety, efficacy or pharmacokinetic characteristics. If FDA determines that the safety or efficacy data included in any marketing application we submit do not warrant marketing approval for the affected product or product candidate, we may be required to conduct additional preclinical studies or clinical trials, which could be costly and time-consuming. Even if we believe we have successfully completed testing, FDA or any equivalent non-U.S. regulatory agency may determine our data is not sufficiently compelling to warrant marketing approval for the indications sought, if at all, and may require us to engage in additional clinical trials or provide further analysis which may be costly and time-consuming. Any adverse events or other data generated during the course of clinical trials of our product candidates and/or clinical trials related to additional indications for our commercialized products could result in action by FDA or an equivalent non-U.S. regulatory agency, which may restrict our ability to sell, or adversely affect sales of, currently marketed products, or such events or other data could otherwise have a material adverse effect on a related commercial product, including with respect to its safety profile. Any failure or delay in completing such clinical trials could materially and adversely affect the maintenance and growth of the markets for the related marketed products, which could adversely affect our business, financial condition, results of operations and overall growth prospects.

In addition to issues relating to the results generated in clinical trials, clinical trials can be delayed or halted for a variety of reasons, including:

- direct and indirect impacts of the evolving effects of the COVID-19 pandemic on various aspects and stages of the clinical development process, including the inherent limitations of remote and virtual approaches, and interruption of key clinical trial activities, such as clinical trial site monitoring, due to limitations on travel, quarantines or social distancing protocols imposed or recommended by federal or state governments, employers and others;
- difficulty identifying, recruiting or enrolling eligible patients, often based on the number of clinical trials, particularly with enrollment criteria targeting the same patient population, and in rare diseases with small patient populations;
- difficulty identifying a clinical development pathway, including viable indications and appropriate clinical trial protocol design, particularly where there is no applicable regulatory precedent;
- delays or failures in obtaining regulatory authorization to commence a trial because of safety concerns of regulators relating to our product candidates or similar product candidates of our competitors or failure to follow regulatory guidelines;
- delays or failures in obtaining clinical materials and manufacturing sufficient quantities of the product candidate for use in trials;
- delays or failures in reaching agreement on acceptable terms with prospective study sites;
- delays or failures in obtaining approval of our clinical trial protocol from an institutional review board, known as an ethics committee in Europe, to conduct a clinical trial at a prospective study site;
- failure of our clinical trials and clinical investigators, including contract research organizations or other third parties assisting us with clinical trials, to satisfactorily perform their contractual duties, meet expected deadlines and comply with FDA and other regulatory agencies' requirements, including good clinical practices;
- unforeseen safety issues;

- inability to monitor patients adequately during or after treatment;
- difficulty monitoring multiple study sites; or
- insufficient funds to complete the trials.

In some jurisdictions such as the EU, initiating phase 3 clinical trials and clinical trials in the pediatric population is subject to a requirement to obtain approval or a waiver from the competent authorities of the EU Member States and/or the EMA. If we do not obtain such approval our ability to conduct clinical trials and obtain marketing authorizations or approvals may be severely impaired and our business may be adversely impacted.

Our ability to recruit and retain patients and principal investigators and site staff who, as health care providers, may have heightened exposure to COVID-19, may adversely impact our clinical trial operations. In light of the evolving effects of the COVID-19 pandemic, we have taken measures to implement remote and virtual approaches, including remote data monitoring where possible, to maintain patient safety and trial continuity and to preserve study integrity. We have seen limited COVID-19-related impact to our mid- and late-stage clinical trial activity, despite delays in initiating trial sites. However, GW had begun to recruit patients for an early-stage clinical trial of Epidiolex in the treatment of Rett syndrome and GW terminated this trial in November 2020 due to severe feasibility challenges arising from COVID-19. We could also see an impact on the ability to supply study drug, report trial results, or interact with regulators, ethics committees or other important agencies due to limitations in regulatory authority employee resources or otherwise. In addition, we rely on contract research organizations or other third parties to assist us with clinical trials, and we cannot guarantee that they will continue to perform their contractual duties in a timely and satisfactory manner as a result of the evolving effects of the COVID-19 pandemic. If these effects become more severe, we could experience significant disruptions to our clinical development timelines, which would adversely affect our business, financial condition, results of operations and growth prospects. In addition, some patients may not be able to comply with clinical trial protocols if quarantines impede patient movement or interrupt healthcare services.

Risks Related to the GW Acquisition

We may not realize the anticipated benefits from the acquisition of GW.

On May 5, 2021, we completed the acquisition of GW. The success of the acquisition will depend, in part, on our ability to realize the anticipated benefits from successfully combining our and GW's historical businesses and the integration of our business practices and operations with GW's so that we can fully realize the anticipated benefits of the acquisition. Epidiolex and the other products and technologies acquired may not be successful or continue to grow at the same rate as if our companies operated independently or they may require significantly greater resources and investments than originally anticipated. Conversely, the liabilities assumed in the transaction could be greater than originally anticipated. In addition, difficulties may arise during the process of combining the operations of our companies that could result in the failure to achieve the synergies or free cash flow that we anticipate, the failure to integrate operations and internal systems, programs and controls, the loss of key employees that may be difficult to replace in the very competitive pharmaceutical field, the failure to harmonize both companies' corporate cultures, and the disruption of each company's ongoing businesses or inconsistencies in standards, controls, procedures and policies that adversely affect our ability to maintain relationships with customers, suppliers, distributors, collaboration partners, clinical trial investigators or managers of our clinical trials. As a result, the anticipated benefits of the acquisition may not be realized fully within the expected timeframe or at all or may take longer to realize or cost more than expected, which could materially and adversely affect our business, financial condition, results of operations and growth prospects.

Risks Related to Our Intellectual Property

It is difficult and costly to protect our proprietary rights, and we may not be able to ensure their protection.

Our commercial success depends in part on obtaining, maintaining and defending intellectual property protection for our products and product candidates, including protection of their use and methods of manufacturing and distribution. Our ability to protect our products and product candidates from unauthorized making, using, selling, offering to sell or importation by third parties depends on the extent to which we have rights under valid and enforceable patents or have adequately protected trade secrets that cover these activities.

The degree of protection to be afforded by our proprietary rights is uncertain because legal means afford only limited protection and may not adequately protect our rights or permit us to gain or keep our competitive advantage. For example:

- our patent applications, or those of our licensors or partners, may not result in issued patents;

- others may independently develop similar or therapeutically equivalent products without infringing our patents, or those of our licensors, such as products that are not covered by the claims of our patents, or for which we do not have adequate exclusive rights under our license agreements;
- our issued patents, or those of our licensors or partners, may be held invalid or unenforceable as a result of legal challenges by third parties or may be vulnerable to legal challenges as a result of changes in applicable law;
- our patents covering certain aspects of our products could be delisted from FDA's publication “Approved Drug Products with Therapeutic Equivalence Evaluations,” or Orange Book, as a result of challenges by third parties before FDA or the courts;
- we or our licensors or partners might not have been the first to invent or file, as appropriate, subject matters covered by our issued patents or pending patent applications or those of our licensors or partners;
- competitors may manufacture products in countries where we have not applied for patent protection or that have a different scope of patent protection or that do not respect our patents; or
- others may be issued patents that prevent the sale of our products or require licensing and the payment of significant fees or royalties.

Patent enforcement generally must be sought on a country-by-country basis, and issues of patent validity and infringement may be judged differently in different countries. Many companies have encountered significant problems in protecting, defending and enforcing intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property rights, particularly those relating to pharmaceuticals, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial cost and divert our efforts and attention from other aspects of our business.

Changes in either the patent laws or in interpretations of patent laws in the U.S. and other countries may diminish the value of our intellectual property portfolio. Even if we are able to obtain patents covering our products and product candidates, any patent may be challenged, and potentially invalidated or held unenforceable, including through patent litigation or through patent office procedures that permit challenges to patent validity. Patents can also be circumvented, potentially including by FDA approval of an ANDA or Section 505(b)(2) application that avoids infringement of our intellectual property.

In June 2021, we received notice from Lupin that it has filed with FDA an ANDA for a generic version of Xywav. The notice from Lupin included a “paragraph IV certification” with respect to ten of our patents listed in FDA’s Orange Book for Xywav on the date of our receipt of the notice. A paragraph IV certification is a certification by a generic applicant that patents covering the branded product are invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the generic product.

On July 28, 2021, we filed a patent infringement suit against Lupin in the United States District Court for the District of New Jersey. The complaint alleges that by filing its ANDA, Lupin has infringed ten of our Orange Book listed patents. We are seeking a permanent injunction to prevent Lupin from introducing a generic version of Xywav that would infringe our patents. As a result of this lawsuit, we expect that a stay of approval of up to 30 months will be imposed by FDA on Lupin's ANDA. In June 2021, FDA recognized seven years of Orphan Drug Exclusivity for Xywav through July 21, 2027. On October 4, 2021, Lupin filed an answer to the complaint and counterclaims asserting that the patents are invalid or not enforceable, and that its product, if approved, will not infringe our patents.

We have settled patent litigation with nine companies seeking to introduce generic versions of Xyrem in the U.S. by granting those companies licenses to launch their generic products (and in certain cases, an authorized generic version of Xyrem) in advance of the expiration of the last of our patents. Notwithstanding our Xyrem patents and settlement agreements, additional third parties may also attempt to introduce generic versions of Xyrem, Xywav or other sodium oxybate products for treatment of cataplexy and/or EDS in narcolepsy that design around our patents or assert that our patents are invalid or otherwise unenforceable. Such third parties could launch a generic or 505(b)(2) product referencing Xyrem before the dates provided in our patents or settlement agreements. For example, we have several method of use patents listed in the Orange Book, that expire in 2033 that cover treatment methods included in the Xyrem label related to a drug-drug interaction, or DDI, with divalproex sodium. Although FDA has stated, in granting a Citizen Petition we submitted in 2016, that it would not approve any sodium oxybate ANDA referencing Xyrem that does not include the portions of the currently approved Xyrem label related to the DDI patents, we cannot predict whether a future ANDA filer, or a company that files a Section 505(b)(2) application for a drug referencing Xyrem, may pursue regulatory strategies to avoid infringing our DDI patents notwithstanding FDA’s response to the Citizen Petition, or whether any such strategy would be successful. Likewise, we cannot predict whether we will be able to maintain the validity of these patents or will otherwise obtain a judicial determination that a generic or other sodium oxybate product, its package insert or the generic sodium oxybate REMS or another separate REMS will infringe any of

our patents or, if we prevail in proving infringement, whether a court will grant an injunction that prevents a future ANDA filer or other company introducing a different sodium oxybate product from marketing its product, or instead require that party to pay damages in the form of lost profits or a reasonable royalty.

Since Xyrem's regulatory exclusivity has expired in the EU, we are aware that generic or hybrid generic applications have been approved by various EU regulatory authorities, and additional generic or hybrid generic applications may be submitted and approved. We cannot predict whether our licensee in the EU will be able to enforce our existing European patents against generic or hybrid generic filers in the EU.

We also currently rely on trade secret protection for several of our products, including Defitelio, and product candidates, including nabiximols. Trade secret protection does not protect information or inventions if another party develops that information or invention independently, and establishing that a competitor developed a product through trade secret misappropriation rather than through legitimate means may be difficult to prove. We seek to protect our trade secrets and other unpatented proprietary information in part through confidentiality and invention agreements with our employees, consultants, advisors and partners. Nevertheless, our employees, consultants, advisors and partners may unintentionally or willfully disclose our proprietary information to competitors, and we may not have adequate remedies for such disclosures. Moreover, if a dispute arises with our employees, consultants, advisors or partners over the ownership of rights to inventions, including jointly developed intellectual property, we could lose patent protection or the confidentiality of our proprietary information, and possibly also lose the ability to pursue the development of certain new products or product candidates.

We have incurred and may in the future incur substantial costs as a result of litigation or other proceedings relating to patents, other intellectual property rights and related matters, and we may be unable to protect our rights to, or commercialize, our products.

Our ability, and that of our partners, to commercialize any approved products will depend, in part, on our ability to obtain patents, enforce those patents and operate without infringing the proprietary rights of third parties. If we choose to go to court to stop a third party from infringing our patents, our licensed patents or our partners' patents, that third party has the right to ask the court or an administrative agency to rule that these patents are invalid and/or should not be enforced. These lawsuits and administrative proceedings are expensive and consume time and other resources, and we may not be successful in these proceedings or in stopping infringement. In addition, the inter partes review process, or IPR, under the Leahy-Smith America Invents Act permits any person, whether they are accused of infringing the patent at issue or not, to challenge the validity of certain patents through a proceeding before the Patent Trial and Appeal Board, or PTAB, of the U.S. Patent and Trademark Office.

There is a risk that a court could decide that our patents or certain claims in our patents are not valid or infringed, and that we do not have the right to stop a third party from using the inventions covered by those claims. In addition, the PTAB may invalidate a patent, as happened with six of our patents covering the Xywav and Xyrem REMS, which were invalidated through the IPR process and delisted from the Orange Book. In addition, even if we prevail in establishing that another product infringes a valid claim of one of our patents, a court may determine that we can be compensated for the infringement in damages, and refuse to issue an injunction. As a result, we may not be entitled to stop another party from infringing our patents for their full term.

Litigation involving patent matters is frequently settled between the parties, rather than continuing to a court ruling, and we have settled patent litigation with all nine Xyrem ANDA filers. The FTC has publicly stated that, in its view, certain types of agreements between branded and generic pharmaceutical companies related to the settlement of patent litigation or the manufacture, marketing and sale of generic versions of branded drugs violate the antitrust laws and has commenced investigations and brought actions against some companies that have entered into such agreements. In particular, the FTC has expressed its intention to take aggressive action to challenge settlements that include an alleged transfer of value from the brand company to the generic company (so-called "pay for delay" patent litigation settlements). The U.S. Congress and state legislatures have also identified pharmaceutical patent litigation settlements as potential impediments to generic competition and have introduced, and in states like California passed, legislation to regulate them. Third party payors have also challenged such settlements on the grounds that they increase drug prices. Because there is currently no precise legal standard with respect to the lawfulness of such settlements, many pharmaceutical companies, including us, have faced extensive litigation over whether patent litigation settlements they have entered into are reasonable and lawful. From June 2020 to October 2021, a number of lawsuits were filed on behalf of purported direct and indirect Xyrem purchasers, alleging that the patent litigation settlement agreements we entered with Hikma and other ANDA filers violate state and federal antitrust and consumer protection laws. For additional information on these lawsuits, see Note 14, Commitments and Contingencies-Legal Proceedings of the Notes to Consolidated Financial Statements, included in Part IV of this Annual Report on Form 10-K. It is possible that additional lawsuits will be filed against us making similar or related allegations. We cannot predict the outcome of these or potential additional lawsuits or government actions; however, if the plaintiffs in the class action complaints were to be successful in their claims, they may be entitled to injunctive relief or we may be required to pay significant monetary damages, which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

Parties to such settlement agreements in the U.S. are required by law to file the agreements with the FTC and the U.S. Department of Justice, or DOJ, for review. Accordingly, we have submitted our patent litigation settlement agreements to the FTC and the DOJ for review. We may receive formal or informal requests from the FTC regarding our ANDA litigation settlements, and there is a risk that the FTC may commence a formal investigation or action against us, which could divert the attention of management and cause us to incur significant costs, regardless of the outcome. Any claim or finding that we or our business partners have failed to comply with applicable laws and regulations could be costly to us and could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

A third party may claim that we or our manufacturing or commercialization partners are using inventions covered by the third party's patent rights, or that we or such partners are infringing, misappropriating or otherwise violating other intellectual property rights, and may go to court to stop us from engaging in our normal operations and activities, including making or selling our products. Such lawsuits are costly and could affect our results of operations and divert the attention of management and development personnel. There is a risk that a court could decide that we or our partners are infringing, misappropriating or otherwise violating third party patent or other intellectual property rights, which could be very costly to us and have a material adverse effect on our business. If we are sued for patent infringement, we would need to demonstrate that our products or methods do not infringe the patent claims of the relevant patent and/or that the patent claims are invalid or unenforceable, which we may not be able to do.

In December 2020, Canopy Growth Corporation, or Canopy, filed a complaint against GW alleging infringement of its patent, U.S. Patent No. 10,870,632. Canopy claims that our extraction process used to produce material used to produce Epidiolex infringes its patent. Canopy seeks a judgment that we have infringed their patent and an award of monetary damages. On July 28, 2021, we filed an answer to the amended complaint, and counterclaims seeking judgment that the '632 patent is invalid and that we have not infringed the patent. In October 2021, the court held a claim construction hearing regarding the disputed terms of the '632 patent. If we were found to infringe upon a patent or other intellectual property right, or if we failed to obtain or renew a license under a patent or other intellectual property right from a third party, or if a third party that we were licensing technologies from was found to infringe upon a patent or other intellectual property rights of another third party, we may be required to pay damages, including damages of up to three times the damages found or assessed, if the infringement is found to be willful, suspend the manufacture of certain products or reengineer or rebrand our products, if feasible, or we may be unable to enter certain new product markets. Litigation, whether filed by us or against us, can be expensive and time consuming to defend and divert management's attention and resources. Our competitive position could suffer as a result. In addition, if we have declined or failed to enter into a valid non-disclosure or assignment agreement for any reason, we may not own the invention or our intellectual property, and our products may not be adequately protected.

With respect to our products and product candidates targeting rare indications, relevant regulatory exclusivities such as orphan drug exclusivity or pediatric exclusivity may not be granted or, if granted, may be limited.

The first NDA applicant with an Orphan Drug Designation for a particular active moiety to treat a specific disease or condition that receives FDA approval is usually entitled to a seven-year exclusive marketing period in the U.S. for that drug, for that indication. We rely in part on this Orphan Drug Exclusivity and other regulatory exclusivities to protect Xywav, Epidiolex, Zepzelca, Sunosi, Defitelio (defibrotide), Vyxeos and, potentially, our other products and product candidates from competitors, and we expect to continue relying in part on these regulatory exclusivities in the future. The duration of our regulatory exclusivity period could be impacted by a number of factors, including FDA's later determination that our request for orphan designation was materially defective, that the manufacturer is unable to supply sufficient quantities of the drug, that the extension of the exclusivity period established by the Improving Regulatory Transparency for New Medical Therapies Act does not apply, or the possibility that we are unable to successfully obtain pediatric exclusivity. There is no assurance that we will successfully obtain Orphan Drug Designation for other products or product candidates or other rare diseases or that a product candidate for which we receive Orphan Drug Designation will be approved, or that we will be awarded orphan drug exclusivity upon approval as, for example, FDA may reconsider whether the eligibility criteria for such exclusivity have been met and/or maintained. Moreover, a drug product with an active moiety that is different from that in our drug candidate or, under limited circumstances, the same drug product, may be approved by FDA for the same indication during the period of marketing exclusivity. The limited circumstances include a showing that the second drug is clinically superior to the drug with marketing exclusivity through a demonstration of superior safety or efficacy or that it makes a major contribution to patient care. In addition, if a competitor obtains approval and marketing exclusivity for a drug product with an active moiety that is the same as that in a product candidate we are pursuing for the same indication before us, approval of our product candidate would be blocked during the period of marketing exclusivity unless we could demonstrate that our product candidate is clinically superior to the approved product. In addition, if a competitor obtains approval and marketing exclusivity for a drug product with an active moiety that is the same as that in a product candidate we are pursuing for a different orphan indication, this may negatively impact the market opportunity for our product candidate. There have been legal challenges to aspects of FDA's regulations and policies concerning the exclusivity provisions of the Orphan Drug Act, including whether two drugs are the same drug product, and future challenges could lead to changes that affect the protections potentially afforded our products in ways that are difficult to predict. In a successful legal challenge, a court invalidated FDA's denial of orphan exclusivity to a

drug on the grounds that the drug was not proven to be clinically superior to a previously approved product containing the same ingredient for the same orphan use. In response to the decision, FDA released a policy statement stating that the court's decision is limited just to the facts of that particular case and that FDA will continue to require the sponsor of a designated drug that is the "same" as a previously approved drug to demonstrate that its drug is clinically superior to that drug upon approval in order to be eligible for orphan drug exclusivity, or in some cases, to even be eligible for marketing approval. In the future, there is the potential for additional legal challenges to FDA's orphan drug regulations and policies, and it is uncertain how such challenges might affect our business.

In the European Union, if a marketing authorization is granted for a medicinal product that is designated an orphan drug, that product is entitled to ten years of marketing exclusivity. We rely in part on this orphan drug exclusivity and other regulatory exclusivities to protect Epidyolex, Vyxeos, Defitelio, and Sunosi. During the period of marketing exclusivity, subject to limited exceptions, no similar medicinal product may be granted a marketing authorization for the orphan indication. There is no assurance that we will successfully obtain Orphan Drug Designation for future rare indications or orphan exclusivity upon approval of any of our product candidates that have already obtained designation. Even if we obtain orphan exclusivity for any product candidate, the exclusivity period can be reduced to six years if at the end of the fifth year it is established that the orphan designation criteria are no longer met or if it is demonstrated that the orphan drug is sufficiently profitable that market exclusivity is no longer justified. Further, a similar medicinal product may be granted a marketing authorization for the same indication notwithstanding our marketing exclusivity if we are unable to supply sufficient quantities of our product, or if the second product is safer, more effective or otherwise clinically superior to our orphan drug. In addition, if a competitor obtains marketing authorization and orphan exclusivity for a product that is similar to a product candidate we are pursuing for the same indication, approval of our product candidate would be blocked during the period of orphan marketing exclusivity unless we could demonstrate that our product candidate is safer, more effective or otherwise clinically superior to the approved product.

Other Risks Related to Our Business and Industry

Changes in the market for directors and officers liability insurance could make it more difficult and more expensive for us to obtain directors and officers liability insurance.

In recent years, the market for directors and officers liability insurance for biopharmaceuticals and life sciences companies has changed in ways adverse to us. The premiums charged for such policies have generally increased and the terms of such policies have generally become less favorable. As a result, it is currently expensive and may become significantly more expensive for us to maintain directors and officers liability insurance, and we may be required to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. In any event, there can be no assurance that directors and officers liability insurance will be adequate to cover our potential liabilities or will be generally available to us in the future or, if available, that the cost of such insurance will be commercially justifiable. The increased cost and decreased availability of directors and officers liability insurance could make it more difficult for us to attract and retain qualified persons to serve on our board of directors or as executive officers, and could also make it more difficult and more expensive for us to negotiate and consummate future corporate development transactions, all of which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

Our business is currently adversely affected and could be materially and adversely affected in the future by the evolving effects of the COVID-19 pandemic and related global economic slowdown, including with respect to our commercialization efforts, clinical trial activity, research and development activities, supply chain and corporate development activities and other business operations.

The COVID-19 pandemic continues to have a significant impact on the global healthcare delivery system. Many healthcare systems have had to restructure operations to prioritize caring for COVID-19 patients and limit or cease other activities. The severe burden on healthcare systems caused by this pandemic has impaired the ability to diagnose and treat patients with non-COVID-19 related conditions and impaired the ability of many clinical research sites to start new studies, enroll new patients and monitor patients in clinical trials. Health care provider offices and institutions have experienced workforce disruption, including the inability to hire staff and challenges maintaining appropriate staffing. The lack of access to health care providers has caused, and may continue to cause, delays in appropriate diagnosis, treatment and ongoing care for some patients, which could subsequently impact prescribing and use of our products. The evolving effects of the COVID-19 pandemic and government measures taken in response have had a significant impact, both direct and indirect, on businesses and commerce, as significant reductions in business related activities have occurred, supply chains have been disrupted, and manufacturing and clinical development activities have been curtailed or suspended.

Continued remote work policies, quarantines, shelter-in-place and similar government orders, shutdowns or other restrictions on the conduct of business operations related to the effects of the COVID-19 pandemic may materially and adversely affect our business, our ability to generate sales of our approved products, our supply chain, regulatory, clinical

development and corporate development activities. With respect to our commercialization activities, the evolving effects of the COVID-19 pandemic continue to have a negative impact on demand, new patient starts and treatments for our products, primarily due to the inherent limitations of telemedicine and a reprioritization of healthcare resources toward COVID-19. Due to the nature of the pandemic, we are not able to accurately predict the duration or extent of these impacts on demand for our products. Beginning in March 2020, we transitioned our field-based sales, market access, reimbursement and medical employees out of the field and suspended work-related travel and in-person customer interactions. We utilized technology to continue to engage healthcare professionals and other customers virtually to support patient care. In late June 2020, as clinics and institutions began to allow in-person interactions pursuant to local health authority and government guidelines, our field teams resumed in-person interactions with healthcare professionals and clinics combined with virtual engagement. The level of renewed in-person engagement varies by account, region and country and may be adversely impacted in the future as a result of the continuing impact of the COVID-19 pandemic. The absence of in-person interactions has had a negative impact our ability to effectively communicate product benefits to physicians, limiting their awareness and understanding and use of our products.

For Xywav and Xyrem, COVID-19 protocols and staffing shortages at sleep labs across the U.S. have resulted in reduced access to sleep testing. Since the end of the first quarter of 2020, we have seen a decline in prescribers' ability to diagnose new narcolepsy patients and a related overall decline in new patients starting on therapy. Although patient persistence and compliance with oxybate therapy remained steady during 2021, we continue to expect that delays in obtaining a narcolepsy diagnosis will have a negative impact on new Xywav and Xyrem patient enrollments in future quarters. We believe these dynamics have negatively impacted new patient starts in the U.S. For Sunosi, the impact on demand has been primarily related to the reduced ability of our field-based teams to interact with prescribers and patients' inability to meet with health care providers during this time. As a result, we have seen slower than expected growth of Sunosi prescribers and new patient starts in the U.S. We also anticipate that pricing and reimbursement reviews by certain European regulatory authorities may take longer in certain countries due to the pandemic, which could delay our rolling Sunosi launch and growth prospects for Vyxeos and Epidyolex in those EU member states. In addition, due to the ongoing impacts of the COVID-19 pandemic, we continue to expect a negative impact on demand for and utilization of Defitelio and Vyxeos.

We have also seen an upward trend in demand for patient assistance programs since the end of the first quarter of 2020. In this regard, total revenue bottle volume on a combined basis for Xywav and Xyrem decreased by 1% in the year ended December 31, 2021, compared to the same period in 2020 reflecting our continued investment in patient access programs during the launch of Xywav. Depending on the ultimate duration and severity of the COVID-19 pandemic and the extent of a global economic slowdown, widespread unemployment and resulting loss of employer-sponsored insurance coverage or other market dynamics, we may experience an increasing shift from commercial payor coverage to government payor coverage or increasing demand for patient assistance and/or free drug programs, which could continue to adversely affect net product sales.

In addition, the COVID-19 pandemic continues to rapidly evolve and has resulted in significant volatility in the global financial markets. If this volatility persists and deepens, we could experience an inability to access additional capital or our liquidity could otherwise be impacted, which could in the future negatively affect our capacity for certain corporate development transactions or our ability to make other important, opportunistic investments. In addition, the current recession or additional market corrections resulting from the impact of the evolving effects of the COVID-19 pandemic could materially affect our business and the value of our ordinary shares. While we expect these effects to adversely affect our business operations and financial results, the extent of the impact on our ability to generate sales of our approved products, execute on new product launches, our clinical development and regulatory efforts, our corporate development objectives and the value of and market for our ordinary shares, will depend on future developments that are highly uncertain and cannot be predicted with confidence at this time. Such developments include continued spread of the Delta and Omicron variants in the U.S. and other countries and the potential emergence of other SARS-CoV-2 variants that may prove especially contagious or virulent, the ultimate duration and severity of the pandemic, governmental "stay-at-home" orders and travel restrictions, quarantines, social distancing and business closure requirements in the U.S., Ireland and other countries, and the effectiveness of vaccination programs and other actions taken globally to contain and treat the disease. For example, the inability of our workforce to return to office and field-based work and the ongoing stress and reprioritization within the healthcare systems in our key markets may require us to reassess the timing and scope of key business activities for 2022, including with respect to our ability to continue the launch momentum for Epidiolex, Sunosi, Xywav, Zepzelca and Rylaze. These effects could materially and adversely affect our business, financial condition, results of operations and growth prospects, as further described in the risks and uncertainties described elsewhere in this ''Risk Factors'' section.

We have substantially expanded our international footprint and operations, and we may expand further in the future, which subjects us to a variety of risks and complexities which, if not effectively managed, could negatively affect our business.

We are headquartered in Dublin, Ireland and have offices in multiple locations, including the U.S., the U.K., Italy and Canada. We may further expand our international operations into other countries in the future, either organically or by

acquisition. Conducting our business in multiple countries subjects us to a variety of risks and complexities that may materially and adversely affect our business, results of operations, financial condition and growth prospects, including:

- the diverse regulatory, financial and legal requirements in the countries where we are located or do business, and any changes to those requirements;
- the impact of Brexit on trade relations between the EU and the U.K.;
- challenges inherent in efficiently managing employees in diverse geographies, including the need to adapt systems, policies, benefits and compliance programs to differing labor and employment law and other regulations, as well as maintaining positive interactions with our unionized employees;
- costs of, and liabilities for, our international operations, products or product candidates; and
- public health risks, such as the COVID-19 pandemic and potential related effects on supply chain, travel and employee health and availability.

In addition, there can be no guarantee that we will effectively manage the increasing, global complexity of our business without experiencing operating inefficiencies or control deficiencies. Our failure to do so could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

The U.K.'s withdrawal from the EU, commonly referred to as Brexit, could increase our cost of doing business, reduce our gross margins or otherwise negatively impact our business and our financial results.

Brexit continues to create uncertainty concerning the future relationship between the U.K. and the EU, following the U.K. withdrawal from the EU in January 2020. We have a commercial manufacturing facility in the U.K. at Kent Science Park, and multiple offices in England. Since a significant portion of the regulatory framework in the U.K. is derived from EU laws, Brexit materially impacts the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our product candidates in the U.K. or the EU. In this regard, in December 2020, the EU and U.K. reached an agreement in principle on the framework for their future relationship, the EU-U.K. Trade and Cooperation Agreement, or TCA. Among the changes that have had a direct impact are that Great Britain (England, Scotland and Wales) will be treated as a "third country," a country that is not a member of the EU and whose citizens do not enjoy the EU right to free movement. Northern Ireland continues to follow many aspects of the EU regulatory rules, particularly in relation to trade in goods. As part of the TCA, the EU and the U.K. will recognize GMP inspections carried out by the other party and the acceptance of official GMP documents issued by the other party. The TCA also encourages, although it does not oblige, the parties to consult one another on proposals to introduce significant changes to technical regulations or inspection procedures. Among the areas of absence of mutual recognition are batch testing and batch release. The U.K. has unilaterally agreed to accept EU batch testing and batch release for a period of at least 2 years until January 1, 2023. However, the EU continues to apply EU laws that require batch testing and batch release to take place in the EU territory. This means that medicinal products that are tested and released in the U.K. must be retested and re-released when entering the EU market for commercial use. As it relates to marketing authorizations, Great Britain has introduced a separate regulatory submission process, approval process and a separate national marketing authorization. Northern Ireland, however, continues to be covered by the marketing authorizations granted by the EC. Therefore, our medicine candidates require a separate marketing authorization for Great Britain, which involves additional administrative burden. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, could prevent us from or delay us commercializing our medicine candidates in the U.K. and/or the European Economic Area, or EEA, and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the U.K. and/or EEA for our medicine candidates, which could significantly and materially harm our business. In addition, the EU's regulatory environment for clinical trials has been harmonized as part of the Clinical Trials Regulation from January 31, 2022, but it is currently unclear as to what extent the U.K. will seek to align its regulations with the EU. Failure of the U.K. to closely align its regulations with the EU may have an effect on the cost of conducting clinical trials in the U.K. as opposed to other countries and/or make it harder to seek a marketing authorization for our medicine candidates in the EEA on the basis of clinical trials conducted in the U.K. In the short term there is a risk of disrupted import and export processes due to a lack of administrative processing capacity by the respective U.K. and EU customs agencies that may delay time-sensitive shipments and may negatively impact our product supply chain. All of these changes could increase our costs and otherwise adversely affect our business.

Significant disruptions of information technology systems or data security breaches could adversely affect our business.

In the ordinary course of our business, we collect, store, process and transmit large amounts of confidential information, including intellectual property, proprietary business information and personal data. We have also outsourced some of our operations (including parts of our information technology infrastructure) to a number of third party vendors who may have, or could gain, access to our confidential information. In addition, many of those third parties, in turn, subcontract or outsource some of their responsibilities to third parties.

Our information technology systems, and those of our vendors, are large and complex and store large amounts of confidential information. The size and complexity of these systems make them potentially vulnerable to service interruptions or to security breaches from inadvertent or intentional actions by our employees, third party vendors and/or business partners, or from cyber-attacks by malicious third parties. Attacks of this nature are increasing in frequency, persistence, sophistication and intensity, and are being conducted by sophisticated and organized 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. In addition to the extraction of important information, such attacks could include the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of our information. Although the aggregate impact on our operations and financial condition has not been material to date, we and our vendors have been the target of events of this nature and expect them to continue.

Significant disruptions of our, our third party vendors' and/or business partners' information technology systems or security breaches, including in our remote work environment as a result of the COVID-19 pandemic, could adversely affect our business operations and/or result in the loss, misappropriation, and/or unauthorized access, use or disclosure of, or the prevention of access to, confidential information (including trade secrets or other intellectual property, proprietary business information and personal data), and could result in financial, legal, business and reputational harm to us. Any such event that leads to unauthorized access, use or disclosure of personal data, including personal data regarding our patients or employees, could harm our reputation, compel us to comply with federal and/or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, require us to verify the correctness of database contents and otherwise subject us to liability under laws and regulations that protect the privacy and security of personal data. This could disrupt our business, result in increased costs or loss of revenue, and/or result in significant legal and financial exposure. In addition, security breaches and other inappropriate access can be difficult to detect, and any delay in identifying them may further harm us. Moreover, the prevalent use of mobile devices to access confidential information increases the risk of security breaches. While we have implemented security measures to protect our information technology systems and infrastructure, there can be no assurance that such measures will prevent service interruptions or security breaches that could adversely affect our business. In addition, failure to maintain effective internal accounting controls related to security breaches and cybersecurity in general could impact our ability to produce timely and accurate financial statements and subject us to regulatory scrutiny.

We are subject to significant ongoing regulatory obligations and oversight, which may result in significant additional expense and limit our ability to commercialize our products.

FDA and Equivalent Non-U.S. Regulatory Authorities

Our activities are subject to extensive regulation encompassing the entire life cycle of our products, from research and development activities to marketing approval (including specific post-marketing obligations), manufacturing, labeling, packaging, adverse event and safety reporting, storage, advertising, promotion, sale, pricing and reimbursement, recordkeeping, distribution, importing and exporting. The failure by us or any of our third party partners, including our corporate development and collaboration partners, clinical trial sites, suppliers, distributors and our central pharmacy for Xywav and Xyrem, to comply with applicable requirements could subject us to administrative or judicial sanctions or other negative consequences, such as delays in approval or refusal to approve a product candidate, restrictions on our products, our suppliers, our other partners or us, the withdrawal, suspension or variation of product approval or manufacturing authorizations, untitled letters, warning letters, fines and other monetary penalties, unanticipated expenditures, product recall, withdrawal or seizure, total or partial suspension of production or distribution, interruption of manufacturing or clinical trials, operating restrictions, injunctions, suspension of licenses, civil penalties and/or criminal prosecution, any of which could result in a significant drop in our revenues from the affected products and harm to our reputation and could have a significant impact on our sales, business and financial condition.

We monitor adverse events resulting from the use of our products, as do the regulatory authorities, and we file periodic reports with the authorities concerning adverse events. The authorities review these events and reports, and if they determine that any events and/or reports indicate a trend or signal, they can require a change in a product label, restrict sales and marketing and/or require conduct or other actions, potentially including variation, withdrawal or suspension of the marketing authorization, any of which could result in reduced market acceptance and demand for our products, could harm our reputation and our ability to market our products in the future, and could have a material adverse effect on our business, financial condition, results of operations and growth prospects. FDA, the competent authorities of the EU member states on behalf of the EMA, and the competent authorities of other European countries, also periodically inspect our records related to safety reporting. The EMA's Pharmacovigilance Risk Assessment Committee may propose to the Committee for Medicinal Products for Human Use that the marketing authorization holder be required to take specific steps or advise that the existing marketing authorization be varied, suspended or revoked. Failure to adequately and promptly correct the observation(s) can result in further regulatory enforcement action, which could include the variation, suspension or withdrawal of marketing authorization or imposition of financial penalties or other enforcement measures.

Defibrotide, Vyxeos, Epidyolex and Sativex are available on a named patient basis or through a compassionate use process in many countries where they are not commercially available. If any such country's regulatory authorities determine that we are promoting such products without proper authorization, we could be found to be in violation of pharmaceutical advertising laws or the regulations permitting sales under named patient programs. In that case, we may be subject to financial or other penalties. Any failure to maintain revenues from sales of products on a named patient basis and/or to generate revenues from commercial sales of these products exceeding historical sales on a named patient basis could have an adverse effect on our business, financial condition, results of operations and growth prospects.

FDA, the competent authorities of the EU member states and other European countries, and other governmental authorities require advertising and promotional materials to be truthful and not misleading, and products to be marketed only for their approved indications and in accordance with the provisions of the approved label. Regulatory authorities actively investigate allegations of off-label promotion in order to enforce regulations prohibiting these types of activities. A determination that we have promoted an approved product for off-label uses could subject us to significant liability, including civil and administrative financial penalties and other remedies as well as criminal financial penalties, other sanctions and imprisonment. Even if we are not determined to have engaged in off-label promotion, an allegation that we have engaged in such activities could have a significant impact on our sales, business and financial condition. The U.S. government has also required companies to enter into complex corporate integrity agreements and/or non-prosecution agreements that impose significant reporting and other burdens on the affected companies. Failure to maintain a comprehensive and effective compliance program, and to integrate the operations of acquired businesses into a combined comprehensive and effective compliance program on a timely basis, could subject us to a range of regulatory actions and/or civil or criminal penalties that could affect our ability to commercialize our products and could harm or prevent sales of the affected products, or could substantially increase the costs and expenses of commercializing and marketing our products.

Other Regulatory Authorities

We are also subject to regulation by other regional, national, state and local agencies, including the DEA, the DOJ, the FTC, the United States Department of Commerce, the Office of Inspector General of the U.S. Department of Health and Human Services, or OIG, and other regulatory bodies, as well as similar governmental authorities in those non-U.S. countries in which we commercialize our products.

We are subject to numerous fraud and abuse laws and regulations globally and our sales, marketing, patient support and medical activities may be subject to scrutiny under these laws and regulations. These laws are described in "Business—Government Regulation" in Part I, Item 1 of this Annual Report on Form 10-K. While we maintain a comprehensive compliance program to try to ensure that our practices and the activities of our third-party contractors and employees fall within the scope of available statutory exceptions and regulatory safe harbors whenever possible, and otherwise comply with applicable laws, regulations or guidance, regulators and enforcement agencies may disagree with our assessment or find fault with the conduct of our employees or contractors. In addition, existing regulations are subject to regulatory revision or changes in interpretation by the DOJ or OIG. For example, in November 2020, the U.S. Department of Health and Human Services finalized a previously abandoned proposal to amend the discount safe harbor regulation of the federal anti-kickback statute in a purported effort to create incentives to manufacturers to lower their list prices, and to lower federal program beneficiary out-of-pocket costs. The rule, which is currently slated to take full effect January 1, 2023, revises the discount safe harbor to exclude manufacturer rebates to Medicare Part D plans, either directly or through PBMs, creates a new safe harbor for point-of-sale price reductions that are set in advance and are available to the beneficiary at the point-of-sale, and creates a new safe harbor for service fees paid by manufacturers to PBMs for services rendered to the manufacturer. The effective date of the rule was already delayed by the Biden Administration and legal challenges. It is unclear whether the rule will be further delayed, rewritten, or allowed to go into effect, and if so, what the effect of the rule will be on negotiations of coverage for our products with Medicare Part D plans, or whether the rule will affect our coverage arrangements with commercial insurers. It is also unclear whether the rule will have the intended effect of reducing net prices and beneficiary out-of-pocket costs without also increasing Medicare Part D premiums, which may impact the willingness of Part D plans to cover our products and the price concessions or other terms the plans or their PBMs may seek from us. In addition, in November 2020, the OIG issued a Special Fraud Alert to highlight certain inherent fraud and abuse risks associated with speaker fees, honorariums and expenses paid by pharmaceutical and medical device companies to healthcare professionals participating in company-sponsored events. The Special Fraud Alert sent a clear signal that speaker programs will be subject to potentially heightened enforcement scrutiny.

Many companies have faced government investigations or lawsuits by whistleblowers who bring a *qui tam* action under the False Claims Act on behalf of themselves and the government for a variety of alleged improper marketing activities, including providing free product to customers expecting that the customers would bill federal programs for the product, providing consulting fees, grants, free travel and other benefits to physicians to induce them to prescribe the company's products, and inflating prices reported to private price publication services, which are used to set drug reimbursement rates under government healthcare programs. In addition, the government and private whistleblowers have pursued False Claims Act cases against pharmaceutical companies for causing false claims to be submitted as a result of the marketing of their products

for unapproved uses or violations of the federal anti-kickback statute. If we become the subject of a government False Claims Act or other investigation or whistleblower suit, we could incur substantial legal costs (including settlement costs) and business disruption responding to such investigation or suit, regardless of the outcome.

Public reporting under the Physician Payment Sunshine Act, or Sunshine provisions, and other similar state laws, the requirements of which are discussed in "Business—Government Regulation" in Part I, Item 1 of this Annual Report on Form 10-K, has resulted in increased scrutiny of the financial relationships between industry, teaching hospitals, physicians and other health care providers. Such scrutiny may negatively impact our ability to engage with physicians and other health care providers on matters of importance to us. In addition, government agencies and private entities may inquire about our marketing practices or pursue other enforcement activities based on the disclosures in those public reports. If the data reflected in our reports are found to be in violation of any of the Sunshine provisions or any other U.S. federal, state or local laws or regulations that may apply, or if we otherwise fail to comply with the Sunshine provisions or similar requirements of state or local regulators, we may be subject to significant civil, and administrative penalties, damages or fines.

We have various programs to help patients access our products, including patient assistance programs, which include co-pay coupons for certain of our products, assistance to help patients determine their insurance coverage for our products, and a free product program. Co-pay coupon programs for commercially insured patients, including our program for Xyrem, have received negative publicity related to allegations regarding their use to promote branded pharmaceutical products over other less costly alternatives, and some states have imposed restrictions on manufacturer co-pay programs when therapeutic equivalents are available. In September 2014, the OIG issued a Special Advisory Bulletin warning manufacturers that they may be subject to sanctions under the federal Anti-Kickback Statute and other laws if they do not take appropriate steps to exclude Medicare Part D beneficiaries from using co-pay coupons. It is possible that changes in insurer policies regarding co-pay coupons and/or the introduction and enactment of new legislation or regulatory action could restrict or otherwise negatively affect these patient support programs, which could result in fewer patients using affected products, including Xyrem, and therefore could have a material adverse effect on our sales, business and financial condition.

We have established programs to consider grant applications submitted by independent charitable organizations, including organizations that provide co-pay support to patients who suffer from the diseases treated by our drugs. The OIG has issued guidance for how pharmaceutical manufacturers can lawfully make donations to charitable organizations who provide co-pay assistance to Medicare patients, provided that such organizations, among other things, are *bona fide* charities, are entirely independent of and not controlled by the manufacturer, provide aid to applicants on a first-come basis according to consistent financial criteria, and do not link aid to use of a donor's product. In April 2019, we finalized our civil settlement agreement with the DOJ and OIG and entered into a corporate integrity agreement requiring us to maintain our ongoing corporate compliance program and obligating us to implement or continue, as applicable, a set of defined corporate integrity activities for a period of five years from the effective date of the corporate integrity agreement. These obligations are being extended to the GW legacy organization as part of ongoing integration efforts, and we are working with OIG in that regard. Although we have structured our programs to follow available guidance and the requirements of our corporate integrity agreement, including with regard to our ongoing integration of GW, if we or our vendors or donation recipients are deemed to fail to comply with relevant laws, regulations or evolving government guidance in the operation of these programs, such facts could be used as the basis for an enforcement action against us by the federal government or other enforcement agencies or private litigants, or we could become liable for payment of certain stipulated penalties or could be excluded from participation in federal health care programs, which would have a material adverse effect on our sales, business and financial condition.

We may also become subject to similar investigations by other state or federal governmental agencies or offices of our patient assistance programs or other business practices, which could result in damages, fines, penalties, exclusion from participation in federal health care programs or other criminal, civil or administrative sanctions or enforcement actions, as well as negative publicity, reduction in demand for, or patient access to, our products and/or reduced coverage of our products, including by federal and state health care programs. If any or all of these events occur, our business, financial condition, results of operations and stock price could be materially and adversely affected.

Our business activities outside of the U.S. are subject to the U.S. Foreign Corrupt Practices Act, or FCPA, and similar anti-bribery or anti-corruption laws, regulations or rules of other countries in which we operate, including the U.K. Bribery Act of 2010, or the U.K. Bribery Act. In certain countries, the health care providers who prescribe pharmaceuticals are employed by their government and the purchasers of pharmaceuticals are government entities; therefore, our dealings with these prescribers and purchasers may be subject to regulation under the FCPA, the U.K. Bribery Act and equivalent national laws in other countries. As an example, recently the U.S. Securities and Exchange Commission and the DOJ have increased their FCPA enforcement activities with respect to pharmaceutical companies. Violation of these laws by us or our suppliers and other third party agents for which we may be liable may result in civil or criminal sanctions, which could include monetary fines, criminal penalties, and disgorgement of past profits, which could have a material adverse impact on our business and financial condition.

Outside the U.S., interactions between pharmaceutical companies and physicians are also governed by strict laws, such as national anti-bribery laws of European countries, national sunshine rules, regulations, industry self-regulation codes of conduct and physicians' codes of professional conduct. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

We are also subject to federal, state, national and international laws and regulations governing the privacy and security of health related and other personal data we collect and maintain (e.g., Section 5 of the Federal Trade Commission Act, the California Consumer Privacy Act, or CCPA, and the EU's General Data Protection Regulation, or GDPR). These laws and regulations are evolving and subject to interpretation, and may impose limitations on our activities or otherwise adversely affect our business. Because of the remote work policies we implemented due to the COVID-19 pandemic, information that is normally protected, including company confidential information, may be less secure. Cybersecurity and data security threats continue to evolve and raise the risk of an incident that could affect our operations or compromise our business information or sensitive personal data, including health data. We may also need to collect more extensive health-related information from our employees to manage our workforce. If we or our third party partners fail to comply or are alleged to have failed to comply with applicable data protection and privacy laws and regulations, and related employment rules, or if we were to experience a data breach involving personal data, we could be subject to government enforcement actions or private lawsuits. In addition, our business could be adversely impacted if our ability to transfer personal data outside of the European Economic Area or Switzerland is restricted, which could adversely impact our operating results. For example, in July 2020, the Court of Justice of the European Union, or the Court of Justice, declared the EC's privacy shield framework between the EU and U.S. was invalid, which could adversely impact our ability to transfer personal data from the EU to the U.S. The Court of Justice further ruled that in order to transfer data outside of the EU, under the existing mechanism known as the Standard Contractual Clauses, or SCCs, the importing country's level of protection must be adequate. If the level of protection in the U.S. or any other importing country is called into question under the SCCs, this could further impact our ability to transfer data outside of the EU or Switzerland. Furthermore, following the U.K.'s exit from the EU, the U.K. became a third country to the EU in terms of personal data transfers. The EC has adopted an Adequacy Decision concerning the level of personal data protection in the U.K. under which personal data may now flow freely from the EU to the U.K. However, personal data transfers from the EU to the U.K. may nevertheless be at a greater risk than before because the Adequacy Decision may be suspended.

In addition, numerous other federal, state, national and international laws and regulations govern the privacy and security of the personal data we collect and maintain, including data breach notification laws, state health information and/or genetic privacy laws, federal and state consumer protection laws (e.g., Section 5 of the Federal Trade Commission Act, and the CCPA), and laws outside of the United States that may apply to us, such as the GDPR and other country laws. Many of these laws and regimes, across countries but even within the United States, differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. Compliance with these laws is difficult, constantly evolving, and time consuming. International regulators, federal regulators, state attorneys general, and plaintiffs' attorneys, including class action attorneys, have been and will likely continue to be active in this space.

In California, the CCPA establishes certain requirements for data use and sharing transparency and creates new data privacy rights for California residents. The CCPA and its implementing regulations have already been amended multiple times since their enactment. These laws and regulations are evolving and subject to interpretation, and may impose limitations on our activities or otherwise adversely affect our business. Similarly, there are a number of legislative proposals in the European Union, the United States (at both the federal and state level) as well as in other jurisdictions that could impose new obligations or limitations in areas affecting our business. In addition, some countries are considering or have passed legislation implementing data protection or privacy requirements or requiring local storage and processing of data or similar requirements that could increase the cost and complexity of delivering our services and research activities.

If we or our third party partners fail to comply or are alleged to have failed to comply with these or other applicable data protection and privacy laws and regulations, or if we were to experience a data breach involving personal data, we could be subject to government enforcement actions or private lawsuits. Any associated claims, inquiries, or investigations or other government actions could lead to unfavorable outcomes that have a material impact on our business including through significant penalties or fines, monetary judgments or settlements including criminal and civil liability for us and our officers and directors, increased compliance costs, delays or impediments in the development of new products, negative publicity, increased operating costs, diversion of management time and attention, or other remedies that harm our business, including orders that we modify or cease existing business practices.

If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs, we could be subject to additional reimbursement requirements, penalties, sanctions and fines, which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

We participate in the Medicaid Drug Rebate Program, the 340B program, the U.S. Department of Veterans Affairs, Federal Supply Schedule, or FSS, pricing program, and the Tricare Retail Pharmacy program, and have obligations to report the

average sales price for certain of our drugs to the Medicare program. All of these programs are described in more detail under the heading “Business—Pharmaceutical Pricing, Reimbursement by Government and Private Payors and Patient Access” in Part I, Item 1 of this Annual Report on Form 10-K. For calendar quarters beginning January 1, 2022, manufacturers will need to start reporting the average sales price for drugs under the Medicare program regardless of whether they are enrolled in the Medicaid Drug Rebate Program. Currently, only manufacturers participating in the Medicaid Drug Rebate Program are obligated to do so.

Pricing and rebate calculations vary across products and programs, are complex, and are often subject to interpretation by us, governmental or regulatory agencies and the courts, which can change and evolve over time. In the case of our Medicaid pricing data, if we become aware that our reporting for a prior quarter was incorrect, or has changed as a result of recalculation of the pricing data, we are generally obligated to resubmit the corrected data for up to three years after those data originally were due. Such restatements and recalculations increase our costs for complying with the laws and regulations governing the Medicaid Drug Rebate Program and could result in an overage or underage in our rebate liability for past quarters. Price recalculations also may affect the ceiling price at which we are required to offer our products under the 340B program and give rise to an obligation to refund entities participating in the 340B program for overcharges during past quarters impacted by a price recalculation.

Civil monetary penalties can be applied if we are found to have knowingly submitted any false price or product information to the government, if we are found to have made a misrepresentation in the reporting of our average sales price, if we fail to submit the required price data on a timely basis, or if we are found to have charged 340B covered entities more than the statutorily mandated ceiling price. The Centers for Medicare & Medicaid Services, or CMS, could also decide to terminate our Medicaid drug rebate agreement, in which case federal payments may not be available under Medicaid or Medicare Part B for our covered outpatient drugs. We cannot assure you that our submissions will not be found by CMS to be incomplete or incorrect.

Our failure to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program and other governmental programs could negatively impact our financial results. CMS issued a final regulation, which became effective in April 2016, to implement the changes to the Medicaid Drug Rebate Program under the Affordable Care Act. In December 2020, CMS issued a final regulation that modified prior Medicaid Drug Rebate Program regulations to permit reporting multiple best price figures with regard to value-based purchasing arrangements (beginning in 2022); provide definitions for “line extension,” “new formulation,” and related terms, with the practical effect of expanding the scope of drugs considered to be line extensions that are subject to an alternative rebate formula (beginning in 2022); and revise best price and average manufacturer price exclusions of manufacturer-sponsored patient benefit programs, specifically regarding applicability of such exclusions in the context of pharmacy benefit manager “accumulator” programs (beginning in 2023). The pharmaceutical industry has challenged the provisions of the rule applicable to patient benefit programs in court. It is currently unclear whether CMS will delay or suspend implementation of any of the provisions of this rule or whether any other provisions will become subject to judicial challenge. Regulatory and legislative changes, and judicial rulings relating to the Medicaid Drug Rebate Program and related policies (including coverage expansion), have increased and will continue to increase our costs and the complexity of compliance, have been and will continue to be time-consuming to implement, and could have a material adverse effect on our results of operations, particularly if CMS or another agency challenges the approach we take in our implementation.

The Health Resources and Services Administration, or HRSA, issued a final regulation regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities, which became effective in January 2019. Implementation of this regulation could affect our obligations and potential liability under the 340B program in ways we cannot anticipate. We are also required to report the 340B ceiling prices for our covered outpatient drugs to HRSA, which then publishes them to 340B covered entities. Any charge by HRSA that we have violated this regulation or other requirements of the program could negatively impact our financial results. Moreover, HRSA newly established an administrative dispute resolution, or ADR, process under a final regulation effective January 2021, for claims by covered entities that a manufacturer engaged in overcharging, including claims that a manufacturer limited the ability of a covered entity to purchase the manufacturer’s drugs at the 340B ceiling price, and by manufacturers that a covered entity violated the prohibitions against diversion or duplicate discounts. Such claims are to be resolved through an ADR panel of government officials rendering a decision that could be appealed only in federal court. This ADR regulation has been challenged in separate litigation instituted by PhRMA and by pharmaceutical manufacturers in multiple federal courts. Also, a public notice published in December 2021 by the Office of Management and Budget revealed that HRSA intends to propose a new ADR rule to replace the ADR rule which became effective in January 2021 and that this new rule will propose new requirements and procedures for the 340B program’s ADR process. Under the ADR final rule which became effective in January 2021, an ADR proceeding could potentially subject us to discovery by covered entities and other onerous procedural requirements and could result in additional liability. HRSA could also decide to terminate a manufacturer’s agreement to participate in the 340B program for a violation of that agreement or other good cause shown, in which case the manufacturer’s covered outpatient drugs may no longer be eligible for federal payment under the Medicaid or Medicare Part B program.

Further, legislation may be introduced that, if passed, would, among other things, further expand the 340B program to additional covered entities or would require participating manufacturers to agree to provide 340B discounted pricing on drugs used in an inpatient setting, and any additional future changes to the definition of average manufacturer price or the Medicaid rebate amount could affect our 340B ceiling price calculations and negatively impact our results of operations.

We have obligations to report the average sales price for certain of our drugs to the Medicare program. Statutory or regulatory changes or CMS guidance could affect the average sales price calculations for our products and the resulting Medicare payment rate, and could negatively impact our results of operations.

Pursuant to applicable law, knowing provision of false information in connection with price reporting under the U.S. Department of Veterans Affairs, FSS or Tricare Retail Pharmacy, or Tricare, programs can subject a manufacturer to civil monetary penalties. These program obligations also contain extensive disclosure and certification requirements. If we overcharge the government in connection with our arrangements with FSS or Tricare, we are required to refund the difference to the government. Failure to make necessary disclosures and/or to identify contract overcharges can result in allegations against us under the False Claims Act and other laws and regulations. Unexpected refunds to the government, and responding to a government investigation or enforcement action, would be expensive and time-consuming, and could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

Product liability and product recalls could harm our business.

The development, manufacture, testing, marketing and sale of pharmaceutical products are associated with significant risks of product liability claims or recalls. Side effects or adverse events known or reported to be associated with, or manufacturing defects in, the products sold by us could exacerbate a patient's condition, or could result in serious injury or impairment or even death. This could result in product liability claims against us and/or recalls of one or more of our products. In many countries, including in EU member states, national laws provide for strict (no-fault) liability which applies even where damages are caused both by a defect in a product and by the act or omission of a third party.

Product recalls may be issued at our discretion or at the discretion of our suppliers, government agencies and other entities that have regulatory authority for pharmaceutical sales. Any recall of our products could materially adversely affect our business by rendering us unable to sell that product for some time and by adversely affecting our reputation. A recall could also result in product liability claims by individuals and third party payors. In addition, product liability claims could result in an investigation of the safety or efficacy of our products, our manufacturing processes and facilities, or our marketing programs conducted by FDA, the EC or the competent authorities of the EU member states. Such investigations could also potentially lead to a recall of our products or more serious enforcement actions, limitations on the therapeutic indications for which they may be used, or suspension, variation, or withdrawal of approval. Any such regulatory action by FDA, the EC or the competent authorities of the EU member states could lead to product liability lawsuits as well.

Product liability insurance coverage is expensive, can be difficult to obtain and may not be available in the future on acceptable terms, or at all. Our product liability insurance may not cover all of the future liabilities we might incur in connection with the development, manufacture or sale of our products. A successful claim or claims brought against us in excess of available insurance coverage could subject us to significant liabilities and could have a material adverse effect on our business, financial condition, results of operations and growth prospects. Such claims could also harm our reputation and the reputation of our products, adversely affecting our ability to market our products successfully.

We use hazardous materials in our manufacturing facilities, and any claims relating to the improper handling, storage, release or disposal of these materials could be time-consuming and expensive.

Our operations are subject to complex and increasingly stringent environmental, health and safety laws and regulations in the countries where we operate and, in particular, in Ireland, the U.K. and Italy where we have manufacturing facilities. If an accident or contamination involving pollutants or hazardous substances occurs, an injured party could seek to hold us liable for any damages that result and any liability could exceed the limits or fall outside the coverage of our insurance. We may not be able to maintain insurance with sufficient coverage on acceptable terms, or at all. Costs, damages and/or fines may result from the presence, investigation and remediation of such contamination at properties currently or formerly owned, leased or operated by us or at off-site locations, including where we have arranged for the disposal of hazardous substances or waste. In addition, we may be subject to third party claims, including for natural resource damages, personal injury and property damage, in connection with such contamination.

Risks Related to Controlled Substances

Xyrem, Xywav, Sunosi and nabiximols are controlled substances and certain other cannabis-derived product candidates we are developing may be subject to U.S. federal and state controlled substance laws and regulations, and our failure to comply with these laws and regulations, or the cost of compliance with these laws and regulations, could materially and adversely affect our business, results of operations, financial condition and growth prospects.

Xyrem, Xywav, Sunosi, nabiximols and certain other product candidates we are developing contain controlled substances as defined in the CSA. Controlled substances are subject to a number of requirements and restrictions under the CSA and implementing regulations, including certain registration, security, recordkeeping, reporting, import, export and other requirements administered by the DEA. The DEA classifies controlled substances into five schedules: Schedule I, II, III, IV or V substances. Schedule I substances by definition have a high potential for abuse, no currently "accepted medical use" in the U.S., lack accepted safety for use under medical supervision, and may not be prescribed, marketed or sold in the U.S. Pharmaceutical products approved for use in the U.S. which contain a controlled substance are listed as Schedule II, III, IV or V, with Schedule II substances considered to present the highest potential for abuse or dependence and Schedule V substances the lowest relative risk of abuse among such substances. Schedule I and II drugs are subject to the strictest controls under the CSA, including manufacturing and procurement quotas, heightened security requirements and additional criteria for importation. In addition, dispensing of Schedule II drugs is further restricted. For example, they may not be refilled without a new prescription.

Drug products approved by FDA that contain cannabis or cannabis extracts may be controlled substances and will be rescheduled to Schedules II-V after approval, or, like Epidiolex, removed completely from the schedules by operation of other laws.

Individual states have also established controlled substance laws and regulations. Though state-controlled substances laws often mirror federal law, they may separately schedule our products or our product candidates as well. We or our partners may also be required to obtain separate state registrations, permits or licenses in order to be able to manufacture, distribute, administer or prescribe controlled substances for clinical trials or commercial sale, and failure to meet applicable regulatory requirements could lead to enforcement and sanctions by the states in addition to those from the DEA or otherwise arising under federal law.

U.S facilities conducting research, manufacturing, distributing, importing or exporting, or dispensing controlled substances must be registered (licensed) to perform these activities and must comply with the security, control, recordkeeping and reporting obligations under the CSA, DEA regulations and corresponding state requirements. DEA and state regulatory bodies conduct periodic inspections of certain registered establishments that handle controlled substances. Obtaining and maintaining the necessary registrations and complying with the regulatory obligations may result in delay of the importation, manufacturing, distribution or clinical research of our commercial products and products candidates. Furthermore, failure to maintain compliance with the CSA and DEA and state regulations by us or any of our contractors, distributors or pharmacies can result in regulatory action that could have a material adverse effect on our business, financial condition and results of operations. DEA and state regulatory bodies may seek civil penalties, refuse to renew necessary registrations, or initiate proceedings to restrict, suspend or revoke those registrations. In certain circumstances, violations could lead to criminal penalties.

Schedule I and II substances are subject to DEA's annual manufacturing and procurement quota requirements. The annual quota allocated to us or our contract manufacturers for the active ingredients in our products may not be sufficient to complete clinical trials or meet commercial demand. Consequently, any delay or refusal by the DEA in establishing our, or our contract manufacturers', procurement and/or production quota for controlled substances could delay or stop our clinical trials or product launches, which could have a material adverse effect on our business, results of operations, financial condition and growth prospects.

Nabiximols and other cannabinoid product candidates are currently controlled substances, the use of which may generate public controversy.

Since nabiximols and some of our other product candidates derived from botanical marijuana contain controlled substances, their regulatory approval may generate public controversy. Political and social pressures and adverse publicity could lead to challenges in the approval of, and increased expenses for, nabiximols and our product candidates. These pressures could also limit or restrict the introduction and marketing of nabiximols and our product candidates. Adverse publicity from cannabis misuse or adverse side effects from cannabis or other cannabinoid products may adversely affect the commercial success or market penetration achievable by nabiximols and our other cannabinoid product candidates. The nature of our business attracts a high level of public and media interest, and in the event of any resultant adverse publicity, our reputation may be harmed.

Our ability to research, develop and commercialize Epidiolex, nabiximols and certain of our product candidates is dependent on our ability to maintain licenses relating to the cultivation, possession and supply of botanical cannabis, a controlled substance.

Our cannabinoid research and manufacturing facilities are located exclusively in the U.K. In the U.K., licenses to cultivate, possess and supply cannabis for medical research are granted by the Home Office on an annual basis. Although the Home Office has renewed our licenses each year since 1998, it may not do so in the future, in which case we may not be in a position to carry on our research and development program in the U.K. In addition, we are required to maintain our existing commercial licenses to cultivate, produce and supply cannabis. However, if the Home Office were not prepared to renew such licenses, we would be unable to manufacture and distribute our products on a commercial basis in the U.K. or beyond. In order to carry out research in countries other than the U.K., similar licenses to those outlined above are required to be issued by the relevant authority in each country. In addition, we will be required to obtain licenses to export from the U.K. and to import into the recipient country. To date, we have obtained necessary import and export licenses to over 30 countries. Although we have an established track record of successfully obtaining such licenses as required, this may change in the future, which could materially and adversely affect our business, results of operations, financial condition and growth prospects.

Controlled substance legislation differs between countries and legislation in certain countries may restrict or limit our ability to sell Epidyolex, nabiximols and certain of our product candidates.

Most countries are parties to the Single Convention on Narcotic Drugs 1961, which governs international trade and domestic control of narcotic substances, including cannabis extracts. Countries may interpret and implement their treaty obligations in a way that creates a legal obstacle to our obtaining regulatory approval for Epidyolex, nabiximols and certain of our other products in those countries. These countries may not be willing or able to amend or otherwise modify their laws and regulations to permit Epidyolex, nabiximols or certain of our other products to be marketed, or achieving such amendments to the laws and regulations may take a prolonged period of time. In the case of countries with similar obstacles, we would be unable to market Epidyolex, nabiximols and certain of our product candidates in countries in the near future or perhaps at all if the laws and regulations in those countries do not change.

Risks Related to Our Financial Condition and Results

We have incurred substantial debt, which could impair our flexibility and access to capital and adversely affect our financial position, and our business would be adversely affected if we are unable to service our debt obligations.

As of December 31, 2021, we had total indebtedness of approximately $6.4 billion. Our substantial indebtedness may:

- limit our ability to use our cash flow or borrow additional funds for working capital, capital expenditures, acquisitions, investments or other general business purposes;
- require us to use a substantial portion of our cash flow from operations to make debt service payments;
- limit our flexibility to plan for, or react to, changes in our business and industry, or our ability to take specified actions to take advantage of certain business opportunities that may be presented to us;
- expose us to the risk of increased interest rates as certain of our borrowings, including borrowings under the credit agreement, are at variable rates of interest;
- result in dilution to our existing shareholders in the event exchanges of our exchangeable senior notes are settled in our ordinary shares;
- place us at a competitive disadvantage compared to our less leveraged competitors; and
- increase our vulnerability to the impact of adverse economic and industry conditions.

If our cash flows and capital resources are insufficient to fund our debt service obligations, we may be forced to reduce or delay investments and capital expenditures, seek additional capital or restructure or refinance our debt. These alternative measures may not be successful and may not permit us to meet our debt service obligations. In the absence of such cash flows and resources, we could face substantial liquidity problems and might be required to dispose of material assets or operations to meet our debt service and other obligations. In addition, if we are unable to repay amounts under our secured credit agreement or senior secured notes, the credit agreement lenders and note holders could proceed against the collateral granted to them to secure that debt, which would seriously harm our business.

Covenants in our credit agreement and indenture governing our senior secured notes restrict our business and operations in many ways and if we do not effectively manage our covenants, our financial conditions and results of operations could be adversely affected.

The credit agreement and the indenture governing our senior secured notes contain various covenants that, among other things, limit our ability and/or our restricted subsidiaries' ability to:

- incur or assume liens or additional debt or provide guarantees in respect of obligations of other persons;
- pay dividends or distributions or redeem or repurchase capital stock;
- prepay, redeem or repurchase certain debt;
- make loans, investments, acquisitions (including certain acquisitions of exclusive licenses) and capital expenditures;
- enter into agreements that restrict distributions from our subsidiaries;
- enter into transactions with affiliates;
- enter into sale and lease-back transactions;
- sell, transfer or exclusively license certain assets, including material intellectual property, and capital stock of our subsidiaries; and
- consolidate or merge with or into, or sell substantially all of our assets to, another person.

If we undergo a change of control triggering event, we would be required to make an offer to purchase all of the senior secured notes at a purchase price in cash equal to 101% of their principal amount, plus accrued and unpaid interest, subject to certain exceptions. If we engage in certain asset sales, we will be required under certain circumstances to make an offer to purchase the senior secured notes at 100% of the principal amount, plus accrued and unpaid interest.

The credit agreement also includes certain financial covenants that require us to maintain a maximum secured leverage ratio and a minimum interest coverage ratio as long as we have drawn funds under the revolving credit facility (or letters of credit in excess of $50 million have been issued and remain undrawn).

As a result of these restrictions, we may be:

- limited in how we conduct our business;
- unable to raise additional debt or equity financing to operate during general economic or business downturns; or
- unable to compete effectively, take advantage of new business opportunities or grow in accordance with our plans.

Our failure to comply with any of the covenants could result in a default under the credit agreement and the indenture governing our senior secured notes, which, if not cured or waived, could result in us having to repay our borrowings before their due dates. Such default may allow the lenders or the note holders to accelerate the related debt and may result in the acceleration of any other debt to which a cross-acceleration or cross-default provision applies. If we are forced to refinance these borrowings on less favorable terms or if we were to experience difficulty in refinancing the debt prior to maturity, our results of operations or financial condition could be materially affected. In addition, an event of default under the credit agreement may permit the lenders to refuse to permit additional borrowings under the revolving credit facility or to terminate all commitments to extend further credit under the revolving credit facility. Furthermore, if we are unable to repay the amounts due and payable under the credit agreement or senior secured notes, the lenders and note holders may be able to proceed against the collateral granted to them to secure that indebtedness. In the event our lenders or note holders accelerate the repayment of such borrowings, we cannot assure you that we will have sufficient assets to repay such indebtedness.

Moreover, our failure to repurchase our senior secured notes or our exchangeable senior notes at a time when the repurchase is required by the indentures governing our senior secured notes and our exchangeable senior notes or to pay any cash payable on future exchanges of our exchangeable senior notes as required by the indenture governing our exchangeable senior notes, would constitute a default under those indentures.

A default under the indentures governing our exchangeable senior notes could also lead to a default under other debt agreements or obligations, including the credit agreement and indenture governing the senior secured notes. Likewise, a default under the credit agreement or senior secured notes could lead to a default under other debt agreements or obligations, including the indentures governing our exchangeable senior notes.

To continue to grow our business, we will need to commit substantial resources, which could result in future losses or otherwise limit our opportunities or affect our ability to operate and grow our business.

The scope of our business and operations has grown substantially since 2012, including through a series of business combinations and acquisitions. To continue to grow our business over the longer term, we plan to commit substantial resources to product acquisition and in-licensing, product development, clinical trials of product candidates and expansion of our commercial, development, manufacturing and other operations. Acquisition opportunities that we pursue could materially affect our liquidity and capital resources and may require us to incur additional indebtedness, seek equity capital or both. Our ability to raise additional capital may be adversely impacted by potential worsening global economic conditions and the recent disruptions to, and volatility in, the credit and financial markets in the U.S. and worldwide resulting from the effects of the COVID-19 pandemic. In addition, under Irish law, we must have authority from our shareholders to issue any ordinary shares, including ordinary shares that are part of our authorized but unissued share capital. Moreover, as a matter of Irish law, when an Irish public limited company issues ordinary shares to new shareholders for cash, the company must first offer those shares on the same or more favorable terms to existing shareholders on a pro-rata basis, unless this statutory pre-emption obligation is dis-applied, or opted-out of, by approval of its shareholders. At our extraordinary general meeting of shareholders in September 2021, our shareholders voted to approve our proposal to dis-apply the statutory pre-emption obligation on terms that are substantially more limited than our general pre-emption opt-out authority that had been in effect prior to August 4, 2021, which could adversely affect our ability to effectively use our unissued share capital to fund in-licensing or acquisition opportunities, or to otherwise raise additional capital for our business. In any event, an inability to borrow or raise additional capital in a timely manner and on attractive terms could prevent us from expanding our business or taking advantage of acquisition opportunities, and could otherwise have a material adverse effect on our business and growth prospects. In addition, if we use a substantial amount of our funds to acquire or in-license products or product candidates, we may not have sufficient additional funds to conduct all of our operations in the manner we would otherwise choose.

We have significant intangible assets and goodwill. Consequently, the future impairment of our intangible assets and goodwill may significantly impact our profitability.

Our intangible assets and goodwill are significant and are subject to an impairment analysis whenever events or changes in circumstances indicate the carrying amount of the asset may not be recoverable. Additionally, goodwill and indefinite-lived assets are subject to an impairment test at least annually. Events giving rise to impairment are an inherent risk in the pharmaceutical industry and cannot be predicted. For example, in the first quarter of 2020, we recorded a $136.1 million asset impairment charge following the decision to stop enrollment in our Phase 3 clinical study of defibrotide for the prevention of VOD due to a determination that the study is highly unlikely to reach one of its primary endpoints. Our results of operations and financial position in future periods could be negatively impacted should future impairments of intangible assets or goodwill occur.

Our financial results have been and may continue to be adversely affected by foreign currency exchange rate fluctuations.

Because our financial results are reported in U.S. dollars, we are exposed to foreign currency exchange risk as the functional currency financial statements of non-U.S. subsidiaries are translated to U.S. dollars for reporting purposes. To the extent that revenue and expense transactions are not denominated in the functional currency, we are also subject to the risk of transaction losses. For example, because our product sales outside of the U.S. are primarily denominated in the euro, our sales of those products have been and may continue to be adversely affected by fluctuations in foreign currency exchange rates. Given the volatility of exchange rates, as well as our expanding operations, there is no guarantee that we will be able to effectively manage currency transaction and/or translation risks, which could adversely affect our operating results. Although we utilize foreign exchange forward contracts to manage currency risk primarily related to certain intercompany balances denominated in non-functional currencies, our efforts to manage currency risk may not be successful.

Changes in our effective tax rates could adversely affect our business and financial condition, results of operations and growth prospects.

We are incorporated in Ireland and maintain subsidiaries in North America, the U.K. and a number of other foreign jurisdictions. As a result, our effective tax rate is derived from a combination of applicable tax rates in the various jurisdictions where we operate. Our effective tax rate may fluctuate depending on a number of factors, including, but not limited to, the distribution of our profits or losses between the jurisdictions where we operate and changes to or differences in interpretation of tax laws. For example, our income tax expense for the year ended December 31, 2021 included an expense of $259.9 million arising on the remeasurement of our U.K. net deferred tax liability, which arose primarily in relation to the GW Acquisition, due to a change in the statutory tax rate in the U.K. following enactment of the U.K. Finance Act 2021.

We are subject to reviews and audits by the U.S. Internal Revenue Services, or IRS, and other taxing authorities from time to time, and the IRS or other taxing authority may challenge our structure, transfer pricing arrangements and tax positions through an audit or lawsuit. Responding to or defending against challenges from taxing authorities could be expensive and

consume time and other resources. If we are unsuccessful, we may be required to pay taxes for prior periods, interest, fines or penalties, and may be obligated to pay increased taxes in the future, any of which could require us to reduce our operating expenses, decrease efforts in support of our products or seek to raise additional funds. Any of these actions could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

The IRS may not agree with the conclusion that we should be treated as a foreign corporation for U.S. federal tax purposes.

Although we are incorporated in Ireland, the IRS may assert that we should be treated as a U.S. corporation (and, therefore, a U.S. tax resident) for U.S. federal tax purposes pursuant to Section 7874 of the U.S. Internal Revenue Code, or the Code. For U.S. federal tax purposes, a corporation generally is considered a tax resident in the jurisdiction of its organization or incorporation. Because we are an Irish incorporated entity, we would be classified as a foreign corporation (and, therefore, a non-U.S. tax resident) under these rules. Section 7874 of the Code provides an exception under which a foreign incorporated entity may, in certain circumstances, be treated as a U.S. corporation for U.S. federal tax purposes. Because we indirectly acquired all of Jazz Pharmaceuticals, Inc.'s assets through the acquisition of the shares of Jazz Pharmaceuticals, Inc. common stock when the businesses of Jazz Pharmaceuticals, Inc. and Azur Pharma Public Limited Company were combined in a merger transaction in January 2012, or the Azur Merger, the IRS could assert that we should be treated as a U.S. corporation for U.S. federal tax purposes under Section 7874. The IRS continues to scrutinize transactions that are potentially subject to Section 7874, and has issued several sets of final and temporary regulations under Section 7874 since 2012. We do not expect these regulations to affect the U.S. tax consequences of the Azur Merger. Nevertheless, new statutory and/or regulatory provisions under Section 7874 of the Code or otherwise could be enacted that could adversely affect our status as a foreign corporation for U.S. federal tax purposes, and any such provisions could have prospective or retroactive application to us, our shareholders, Jazz Pharmaceuticals, Inc. and/or the Azur Merger.

Our affiliates' ability to use their net operating losses and carryforward tax losses to offset potential taxable income is limited under applicable law and could be subject to further limitations if we do not generate taxable income in a timely manner or if certain "ownership change" provisions of applicable law result in further limitations.

Following certain acquisitions of a U.S. corporation by a foreign corporation, Section 7874 of the Code can limit the ability of the acquired U.S. corporation and its U.S. affiliates to use U.S. tax attributes such as net operating losses, or NOLs, to offset U.S. taxable income resulting from certain transactions. Our U.S. affiliates have a significant amount of NOLs. As a result of Section 7874 of the Code, after the Azur Merger, our U.S. affiliates have not been able and will continue to be unable, for a period of time, to utilize their U.S. tax attributes to offset their U.S. taxable income, if any, resulting from certain taxable transactions. While we expect to be able to fully utilize our U.S. affiliates' U.S. NOLs before they expire, as a result of this limitation, it may take our U.S. affiliates longer to use their NOLs.

Our ability to use these NOLs to offset potential future taxable income and related income taxes that would otherwise be due also depends on our ability to generate future income that is taxable in the U.S. before the NOLs expire. We cannot predict with certainty when, or whether, our U.S. affiliates will generate sufficient taxable income to use all of the NOLs. In addition, the use of NOLs to offset potential future taxable income and related income taxes that would otherwise be due is subject to limitations under the "ownership change" provisions of Sections 382 and 383 of the Code and similar state provisions. Additionally, U.K. carryforward tax losses may become subject to limitations in the event of certain changes in the ownership interest of significant shareholders where there is also a major change in the nature of conduct of a trade or business within a specified period of time. These limitations may cause us to lose or forfeit additional NOLs or carryforward tax losses before we can use these attributes. Subsequent ownership changes and changes to the U.S. federal or state or U.K. tax rules with respect to the use of NOLs and carryforward tax losses may further affect our ability to use these losses in future years.

Changes to tax laws relating to multinational corporations could adversely affect us.

The U.S. Congress, the EU, the Organization for Economic Co-operation and Development, or OECD, and other government agencies in jurisdictions where we and our affiliates do business have had an extended focus on issues related to the taxation of multinational corporations. One example is the OECD's initiative in the area of "base erosion and profit shifting," or BEPS. Many countries have implemented or begun to implement legislation and other guidance to align their international tax rules with the OECD's BEPS recommendations. In addition, the OECD has been working on an extension of the BEPS project, referred to as BEPS 2.0, focusing on (1) global profit allocation and (2) a global minimum tax rate. In particular, the OECD has released a framework proposal reflecting the agreement of over 130 jurisdictions, including Ireland, to implement a global minimum tax rate of 15% for large multinational corporations on a jurisdiction-by-jurisdiction basis by 2023. As a result of the focus on the taxation of multinational corporations, the tax laws in Ireland, the U.S. and other countries in which we and our affiliates do business could change on a prospective or retroactive basis, and any such changes could adversely affect us.

Further, the Biden administration and U.S. Congress continue to consider changes in U.S. tax laws. In April 2021, the Biden administration released the Made in America Tax Plan, which includes significant modifications to key provisions of the existing U.S. corporate income tax regime, including an increase in the U.S. corporate income tax rate and an increase in the tax

rate on certain earnings of controlled foreign corporations. In November 2021, the U.S. House of Representatives passed the "Build Back Better Act" budget reconciliation bill, which proposes significant changes to the U.S. tax treatment of multinational corporations. Congress continues to consider these and other legislative proposals. These changes, if enacted, could adversely impact our tax provision, cash tax liability and effective tax rate. At this stage, it is not possible to predict which, if any, proposals the U.S. Congress will ultimately accept, reject or modify and whether any proposals will be enacted into law.

A substantial portion of our indebtedness bears interest at variable interest rates based on USD LIBOR and certain of our financial contracts are also indexed to USD LIBOR. Changes in the method of determining LIBOR, or the replacement of LIBOR with an alternative reference rate, may adversely affect interest rates on our current or future indebtedness and may otherwise adversely affect our financial condition and results of operations.

In July 2017, the Financial Conduct Authority, or FCA, the authority that regulates the London Inter-bank Offered Rate, or LIBOR, announced that it intended to stop compelling banks to submit rates for the calculation of LIBOR after 2021. FCA also announced that certain of the commonly used USD LIBOR tenors will continue to be published until June 30, 2023; however, the Federal Reserve, Federal Deposit Insurance Corporation and the Office of the Comptroller of Currency in the U.S. as well as the FCA announced that all market participants should stop using LIBOR in new contracts after December 31, 2021, subject to limited exemptions for loans and derivative products. Accordingly, new contracts entered into after December 31, 2021, must utilize an alternative reference rate. We have certain financial contracts, including the credit agreement and our derivative instruments, that are indexed to USD LIBOR. Changes in the method of determining LIBOR, or the replacement of LIBOR with an alternative reference rate, may adversely affect interest rates on our current or future indebtedness. Any transition process may involve, among other things, increased volatility or illiquidity in markets for instruments that rely on LIBOR, reductions in the value of certain instruments or the effectiveness of related transactions such as hedges, increased borrowing costs, uncertainty under applicable documentation, or difficult and costly consent processes. In addition, we have certain financial contracts, including the credit agreement and our derivative instruments, that are indexed to Euro Inter-bank Offered Rate, or EURIBOR (which is based on the average interest rates at which a large panel of European banks borrow funds from one another). There is no indication at this time that EURIBOR will cease to be published in the near future. However, the transition away from LIBOR, and also potentially EURIBOR, may result in increased expenses, may impair our ability to refinance our indebtedness or hedge our exposure to floating rate instruments, or may result in difficulties, complications or delays in connection with future financing efforts, any of which could adversely affect our financial condition and results of operations.

Risks Related to Our Ordinary Shares

The market price of our ordinary shares has been volatile and is likely to continue to be volatile in the future, and the value of your investment could decline significantly.

The stock market in general, including the market for life sciences companies, has experienced extreme price and trading volume fluctuations that have often been unrelated or disproportionate to the operating performance of those companies, which has resulted in decreased market prices, notwithstanding the lack of a fundamental change in the underlying business models of those companies. Worsening economic conditions and other adverse effects or developments may negatively affect the market price of our ordinary shares, regardless of our actual operating performance. The market price for our ordinary shares is likely to continue to be volatile and subject to significant price and volume fluctuations in response to market, industry and other factors, including the risk factors described in this "Risk Factors" section.

Our share price may be dependent upon the valuations and recommendations of the analysts who cover our business. If our results do not meet these analysts' forecasts, the expectations of our investors or the financial guidance we provide to investors in any period, the market price of our ordinary shares could decline. Our ability to meet analysts' forecasts, investors' expectations and our financial guidance is substantially dependent on our ability to maintain or increase sales of our marketed products.

In addition, the market price of our ordinary shares may decline if the effects of our acquisition of GW and other strategic transactions on our financial or operating results are not consistent with the expectations of financial analysts or investors. The market price of our ordinary shares could also be affected by possible sales of our ordinary shares by holders of our exchangeable senior notes who may view our exchangeable senior notes as a more attractive means of equity participation in our company and by hedging or arbitrage trading activity involving our ordinary shares by the holders of our exchangeable senior notes.

We are subject to Irish law, which differs from the laws in effect in the U.S. and may afford less protection to holders of our securities.

It may not be possible to enforce court judgments obtained in the U.S. against us in Ireland based on the civil liability provisions of the U.S. federal or state securities laws. In addition, there is some uncertainty as to whether the courts of Ireland

would recognize or enforce judgments of U.S. courts obtained against us or our directors or officers based on the civil liability provisions of the U.S. federal or state securities laws or hear actions against us or those persons based on those laws. We have been advised that the U.S. currently does not have a treaty with Ireland providing for the reciprocal recognition and enforcement of judgments in civil and commercial matters. Therefore, a final judgment for the payment of money rendered by any U.S. federal or state court based on civil liability, whether or not based solely on U.S. federal or state securities laws, would not automatically be enforceable in Ireland.

As an Irish company, we are governed by the Irish Companies Act 2014, which differs in some material respects from laws generally applicable to U.S. corporations and shareholders, including, among others, differences relating to interested director and officer transactions, mergers, amalgamations and acquisitions, takeovers and shareholder lawsuits. The duties of directors and officers of an Irish company are generally owed to the company only. Shareholders of Irish companies generally do not have a personal right of action against directors or officers of the company and may exercise such rights of action on behalf of the company only in limited circumstances. Accordingly, holders of our securities may have more difficulty protecting their interests than would holders of securities of a corporation incorporated in a U.S. jurisdiction.

Our articles of association, Irish law, our credit agreement and the indentures governing our senior secured notes and exchangeable senior notes contain provisions that could delay or prevent a takeover of us by a third party.

Our articles of association could delay, defer or prevent a third party from acquiring us, despite the possible benefit to our shareholders, or otherwise adversely affect the price of our ordinary shares. In addition to our articles of association, several mandatory provisions of Irish law could prevent or delay an acquisition of us. We are also subject to various provisions of Irish law relating to mandatory bids, voluntary bids, requirements to make a cash offer and minimum price requirements, as well as substantial acquisition rules and rules requiring the disclosure of interests in our shares in certain circumstances. Furthermore, our credit agreement limits our ability to enter into certain fundamental changes, and the indentures governing our senior secured notes and exchangeable senior notes require us to offer to repurchase such notes for cash if we undergo certain fundamental changes. Additionally, in certain circumstances, the indentures governing our exchangeable senior notes require us to increase the exchange rate for a holder of our exchangeable senior notes in connection with a fundamental change. A takeover of us may trigger a default under the credit agreement or the requirement that we offer to purchase our senior secured notes or exchangeable senior notes and/or increase the exchange rate applicable to our exchangeable senior notes, which could make it more costly for a potential acquirer to engage in a business combination transaction with us.

These provisions, whether alone or together, may discourage potential takeover attempts, discourage bids for our ordinary shares at a premium over the market price or adversely affect the market price of, and the voting and other rights of the holders of, our ordinary shares. These provisions, whether alone or together, could also discourage proxy contests and make it more difficult for our shareholders to elect directors other than the candidates nominated by our board.

Future sales and issuances of our ordinary shares, securities convertible into our ordinary shares or rights to purchase ordinary shares or convertible securities could result in additional dilution of the percentage ownership of our shareholders and could cause our share price to decline.

We expect to continue to opportunistically seek access to additional capital to license or acquire additional products, product candidates or companies to expand our operations or for general corporate purposes. To the extent we raise additional capital by issuing equity securities or securities convertible into or exchangeable for ordinary shares, our shareholders may experience substantial dilution. We may sell ordinary shares, and we may sell convertible or exchangeable securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell such ordinary shares, convertible or exchangeable securities or other equity securities in subsequent transactions, existing shareholders may be materially diluted.

We have never declared or paid dividends on our capital stock and we do not anticipate paying dividends in the foreseeable future.

We do not currently plan to pay cash dividends in the foreseeable future. Any future determination as to the payment of dividends will, subject to Irish legal requirements, be at the sole discretion of our board of directors and will depend on our financial condition, results of operations, capital requirements, compliance with the terms of the credit agreement and the indenture governing our senior secured notes, and other factors our board of directors deems relevant. Accordingly, holders of our ordinary shares must rely on increases in the trading price of their shares for returns on their investment in the foreseeable future. In addition, in the event that we pay a dividend on our ordinary shares, in certain circumstances, as an Irish tax resident company, some shareholders may be subject to withholding tax, which could adversely affect the price of our ordinary shares.

General Risk Factors

If we fail to attract, retain and motivate key personnel or to retain the members of our executive management team, our operations and our future growth may be adversely affected.

Our success and our ability to grow depend in part on our continued ability to attract, retain and motivate highly qualified personnel, including our executive management team. In addition, changes we make to our current and future work environments may not meet the needs or expectations of our employees or may be perceived as less favorable compared to other companies' policies, which could negatively impact our ability to hire and retain qualified personnel, whether in a remote or in-office environment. The loss of services and institutional knowledge of one or more additional members of our executive management team or other key personnel could delay or prevent the successful completion of some of our vital activities and may negatively impact our operations and future growth. We do not carry "key person" insurance. In addition, changes in our organization as a result of executive management transition may have a disruptive impact on our ability to implement our strategy. Until we integrate new personnel, and unless they are able to succeed in their positions, we may be unable to successfully manage and grow our business. In any event, if we are unable to attract, retain and motivate quality individuals, or if there are delays, or if we do not successfully manage personnel and executive management transitions, our business, financial condition, results of operations and growth prospects could be adversely affected.

Our business and operations could be negatively affected if we become subject to shareholder activism or hostile bids, which could cause us to incur significant expense, hinder execution of our business strategy and impact our stock price.

Shareholder activism, which takes many forms and arises in a variety of situations, has been increasingly prevalent. Stock price declines due to the evolving effects of the COVID-19 may also increase our vulnerability to unsolicited approaches. If we become the subject of certain forms of shareholder activism, such as proxy contests or hostile bids, the attention of our management and our board of directors may be diverted from execution of our strategy. Such shareholder activism could give rise to perceived uncertainties as to our future strategy, adversely affect our relationships with business partners and make it more difficult to attract and retain qualified personnel. Also, we may incur substantial costs, including significant legal fees and other expenses, related to activist shareholder matters. Our stock price could be subject to significant fluctuation or otherwise be adversely affected by the events, risks and uncertainties of any shareholder activism.

Item 1B. Unresolved Staff Comments

There are no material unresolved written comments that were received from the SEC staff 180 days or more before the end of our 2021 fiscal year relating to our periodic or current reports under the Securities Exchange Act of 1934, as amended.

Item 2. Properties

Our corporate headquarters are located in Dublin, Ireland, and our U.S. operations are located in Palo Alto, California, Carlsbad, California and Philadelphia, Pennsylvania. In addition to our owned manufacturing and development facilities and our leased administrative, manufacturing and development facilities, we also have dedicated growing facilities operated by contract partners. The following table contains information about our significant properties as of December 31, 2021:

Type	Location	Approximate Square Feet	Lease / Contract Expiration Date
Administrative office	Dublin, Ireland	45,000	2036
Administrative office	Palo Alto, United States	99,000	2029
Administrative office	Carlsbad, United States	52,000	2023-2027
Administrative office	Philadelphia, United States	60,000	2029
Administrative office	Oxford, United Kingdom	26,000	2028
Administrative office	Cambridge, United Kingdom	22,000	2030-2031
Administrative office	London, United Kingdom	7,000	2028
Administrative office and laboratory	Villa Guardia (Como), Italy	34,000	2023
Manufacturing and development	Athlone, Ireland	58,000	Owned
Manufacturing and development	Villa Guardia (Como), Italy	45,000	Owned
Manufacturing and development	Southern United Kingdom	150,000	2022-2033
Growing facility	Eastern United Kingdom	1,960,000	2023
Growing facility	Northern United Kingdom	915,000	2022
Growing facility	Southern United Kingdom	165,000	2028
Growing facility under construction	Southern United Kingdom	370,000	2035

In addition, we have offices in Canada, Japan, Australia, France and elsewhere in Europe.

We believe that our existing properties are in good condition and suitable for the conduct of our business. As we continue to expand our operations, we may need to lease additional or alternative facilities.

Item 3. Legal Proceedings

The information required to be set forth under this Item 3 is incorporated by reference to Note 14, Commitments and Contingencies—Legal Proceedings of the Notes to Consolidated Financial Statements, included in Part IV of this Annual Report on Form 10-K.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our ordinary shares trade on The Nasdaq Global Select Market under the trading symbol "JAZZ."

Holders of Ordinary Shares

As of February 22, 2022, there were 907 holders of record of our ordinary shares. Because almost all of our ordinary shares are held by brokers, nominees and other institutions on behalf of shareholders, we are unable to estimate the total number of shareholders represented by these record holders.

Dividends

In 2021 and 2020, we did not declare or pay cash dividends on our common equity. Under Irish law, dividends may only be paid, and share repurchases and redemptions must generally be funded only out of, "distributable reserves." In addition, the terms of our credit agreement restrict our ability to make certain restricted payments, including dividends and other distributions by us in respect of our ordinary shares, subject to, among other exceptions, (1) a general exception for dividends and restricted payments up to $30 million in the aggregate and (2) an exception that allows for restricted payments, subject to a cap equal to the sum of (i) $100 million plus (ii) so long as our secured leverage ratio (as defined in our credit agreement) does not exceed 3:1 after giving pro forma effect to the restricted payment, a formula-based amount tied to our consolidated net income; provided that such cap applies only if our total leverage ratio (as defined in our credit agreement) exceeds 2:1 after giving pro forma effect to the restricted payment. Any future determination as to the payment of dividends will, subject to Irish legal requirements, be at the sole discretion of our board of directors and will depend on our consolidated financial condition, results of operations, capital requirements, compliance with the terms our credit agreement or other future borrowing arrangements, and other factors our board of directors deems relevant.

Unregistered Sales of Equity Securities

Except as previously reported in our Quarterly Reports on Form 10-Q and Current Reports on Form 8-K filed with the Securities and Exchange Commission, or SEC, during the year ended December 31, 2021, there were no unregistered sales of equity securities by us during the year ended December 31, 2021.

Irish Law Matters

As we are an Irish incorporated company, the following matters of Irish law are relevant to the holders of our ordinary shares.

Irish Restrictions on Import and Export of Capital

Except as indicated below, there are no restrictions on non-residents of Ireland dealing in Irish domestic securities, which includes ordinary shares of Irish companies. Dividends and redemption proceeds also continue to be freely transferable to non-resident holders of such securities. The Financial Transfers Act, 1992 gives power to the Minister for Finance of Ireland to restrict financial transfers between Ireland and other countries and persons. Financial transfers are broadly defined and include all transfers that would be movements of capital or payments within the meaning of the treaties governing the member states of the European Union. The acquisition or disposal of interests in shares issued by an Irish incorporated company and associated payments falls within this definition. In addition, dividends or payments on redemption or purchase of shares and payments on a liquidation of an Irish incorporated company would fall within this definition. At present the Financial Transfers Act, 1992 prohibits financial transfers involving the late Slobodan Milosevic and associated persons, Belarus, certain persons indicted by the International Criminal Tribunal for the former Yugoslavia, the late Osama bin Laden, Al-Qaida, the Taliban of Afghanistan, Democratic Republic of Congo, Democratic People's Republic of Korea (North Korea), Iran, Iraq, Côte d'Ivoire, Lebanon, Liberia, Zimbabwe, Sudan, Somalia, Republic of Guinea, Republic of Guinea-Bissau, Afghanistan, Libya, Syria, Tunisia, certain known terrorists and terrorist groups, countries that harbor certain terrorist groups and Ukraine without the prior permission of the Central Bank of Ireland.

Any transfer of, or payment in respect of, a share or interest in a share involving the government of any country that is currently the subject of United Nations sanctions, any person or body controlled by any of the foregoing, or by any person acting on behalf of the foregoing, may be subject to restrictions pursuant to such sanctions as implemented into Irish law.

Irish Taxes Applicable to U.S. Holders

Irish Tax on Dividends. While we have no current plans to pay dividends, dividends on our ordinary shares would generally be subject to Irish Dividend Withholding Tax at the standard rate (currently 25%), unless an exemption applies.

Irish Tax on Capital Gains. A shareholder who is neither resident nor ordinarily resident in Ireland and does not hold our ordinary shares in connection with a trade or business carried on by such shareholder in Ireland through a branch or agency should not be subject to Irish tax on capital gains on a disposal of our ordinary shares.

Capital Acquisitions Tax. Irish capital acquisitions tax, or CAT, is comprised principally of gift tax and inheritance tax. CAT could apply to a gift or inheritance of our ordinary shares irrespective of the place of residence, ordinary residence or domicile of the parties. This is because our ordinary shares are regarded as property situated in Ireland as our share register must be held in Ireland. The person who receives the gift or inheritance has primary liability for CAT.

CAT is levied at a rate of 33% above certain tax-free thresholds. The appropriate tax-free threshold is dependent upon (i) the relationship between the donor and the donee and (ii) the aggregation of the values of previous gifts and inheritances received by the donee from persons within the same category of relationship for CAT purposes. Gifts and inheritances passing between spouses are exempt from CAT. Our shareholders should consult their own tax advisers as to any tax consequences of holding our ordinary shares, including whether CAT is creditable or deductible in computing any domestic tax liabilities.

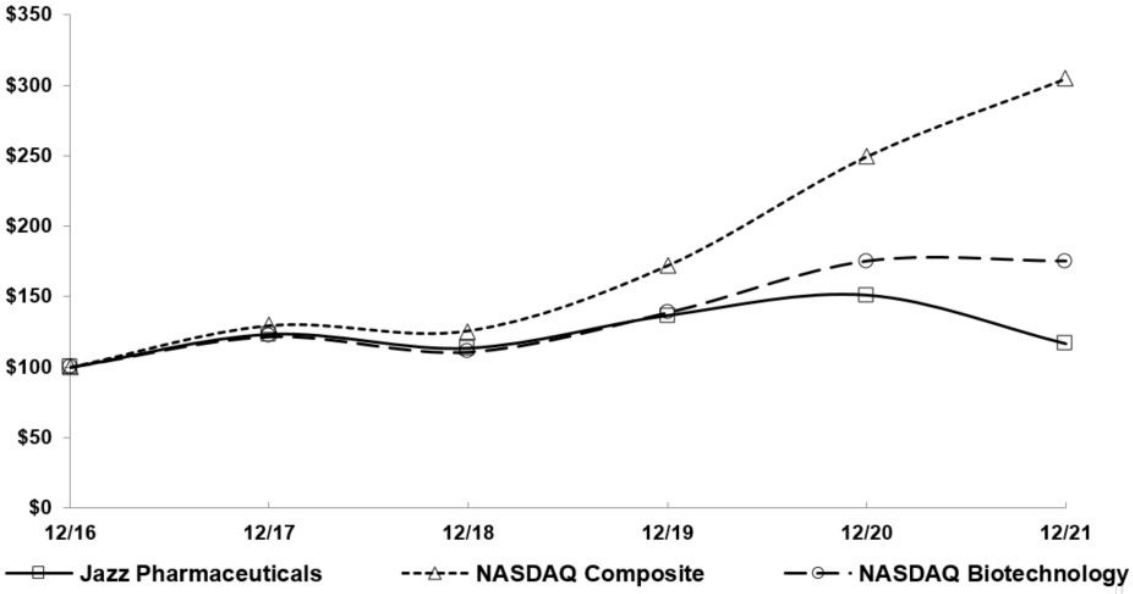
Stamp Duty. Irish stamp duty (if any) may become payable in respect of ordinary share transfers. However, a transfer of our ordinary shares from a seller who holds shares through Depository Trust Company, or DTC, to a buyer who holds the acquired shares through DTC will not be subject to Irish stamp duty. A transfer of our ordinary shares (i) by a seller who holds ordinary shares outside of DTC to any buyer or (ii) by a seller who holds the ordinary shares through DTC to a buyer who holds the acquired ordinary shares outside of DTC, may be subject to Irish stamp duty (currently at the rate of 1% of the price paid or the market value of the ordinary shares acquired, if greater). The person accountable for payment of stamp duty is the buyer or, in the case of a transfer by way of a gift or for less than market value, all parties to the transfer.

A shareholder who holds ordinary shares outside of DTC may transfer those ordinary shares into DTC without giving rise to Irish stamp duty provided that the shareholder would be the beneficial owner of the related book-entry interest in those ordinary shares recorded in the systems of DTC (and in exactly the same proportions) as a result of the transfer and at the time of the transfer into DTC there is no sale of those book-entry interests to a third party being contemplated by the shareholder. Similarly, a shareholder who holds ordinary shares through DTC may transfer those ordinary shares out of DTC without giving rise to Irish stamp duty provided that the shareholder would be the beneficial owner of the ordinary shares (and in exactly the same proportions) as a result of the transfer, and at the time of the transfer out of DTC there is no sale of those ordinary shares to a third party being contemplated by the shareholder. In order for the share registrar to be satisfied as to the application of this Irish stamp duty treatment where relevant, the shareholder must confirm to us that the shareholder would be the beneficial owner of the related book-entry interest in those ordinary shares recorded in the systems of DTC (and in exactly the same proportions) (or vice-versa) as a result of the transfer and there is no agreement being contemplated for the sale of the related book-entry interest or the ordinary shares or an interest in the ordinary shares, as the case may be, by the shareholder to a third party.

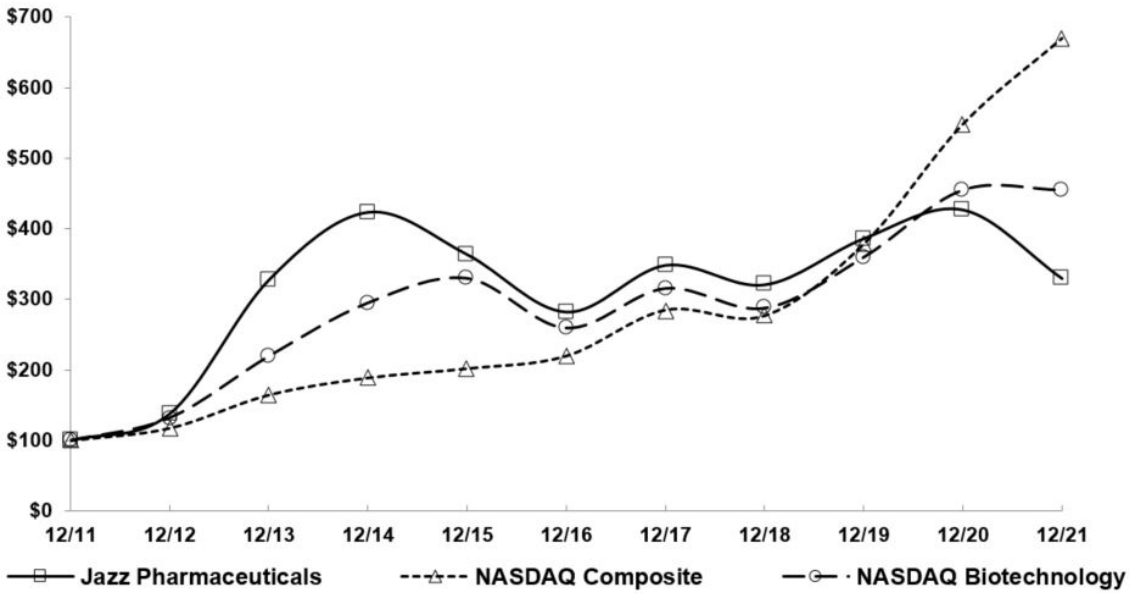
Performance Measurement Comparison (1)

The following graphs show the total shareholder return on the last day of each year of an investment of $100 in cash as if made on December 31, 2016 and December 31, 2011, respectively, in (i) our ordinary shares; (ii) the Nasdaq Composite Index; and (iii) the Nasdaq Biotechnology Index through December 31, 2021. The shareholder return shown in the graphs below are not necessarily indicative of future performance, and we do not make or endorse any predictions as to future shareholder returns.

COMPARISON OF FIVE YEAR CUMULATIVE TOTAL RETURN (2)



COMPARISON OF TEN YEAR CUMULATIVE TOTAL RETURN (2)



(1) This section is not "soliciting material," is not deemed "filed" with the SEC and is not to be incorporated by reference into any of our filings under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, or Exchange Act, whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.

(2) Information used in the graph was obtained from Research Data Group, Inc.

Issuer Purchases of Equity Securities

In November 2016, our board of directors authorized a share repurchase program and as of December 31, 2021 had authorized the repurchase of ordinary shares having an aggregate purchase price of up to $1.5 billion, exclusive of any brokerage commissions. Under this program, which has no expiration date, we may repurchase ordinary shares from time to time on the open market. In 2021, we did not repurchase any of our ordinary shares under the share repurchase program. As of December 31, 2021, the remaining amount authorized under the share repurchase program was $431.2 million.

Under the share repurchase program, we are authorized to repurchase shares from time to time through open market repurchases. Such repurchases may be pursuant to Rule 10b-18 or Rule 10b5-1 agreements as determined by our management and in accordance with the requirements of the Securities and Exchange Commission.

Item 6. Reserved

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

The purpose of the Management Discussion and Analysis is to present information that management believes is relevant to promote a understanding of our results of operations and cash flows for the fiscal year ended December 31, 2021 and our financial condition as of December 31, 2021 and should be read in conjunction with the consolidated financial statements and notes to consolidated financial statements included elsewhere in this Annual Report on Form 10-K. This discussion contains forward-looking statements that involve risks and uncertainties. When reviewing the discussion below, you should keep in mind the substantial risks and uncertainties that impact our business. In particular, we encourage you to review the risks and uncertainties described in "Risk Factors" in Part I, Item 1A in this Annual Report on Form 10-K. These risks and uncertainties could cause actual results to differ materially from those projected in forward-looking statements contained in this report or implied by past results and trends.

Overview

Jazz Pharmaceuticals plc is a global biopharmaceutical company whose purpose is to innovate to transform the lives of patients and their families. We are dedicated to developing life-changing medicines for people with serious diseases - often with limited or no therapeutic options. We have a diverse portfolio of marketed medicines and novel product candidates, from early- to late-stage development, in neuroscience and oncology. Within these therapeutic areas, we strive to identify new options for patients by actively exploring small molecules and biologics, and through innovative delivery technologies and cannabinoid science.

Our strategy for growth is rooted in executing commercial launches and ongoing commercialization initiatives; advancing robust research and development, or R&D, programs and delivering impactful clinical results; effectively deploying capital to strengthen the prospects of achieving our short- and long-term goals through strategic corporate development; and delivering strong financial performance. We focus on patient populations with high unmet needs. We identify and develop differentiated therapies for these patients that we expect will be long-lived assets and that we can support with an efficient commercialization model. In addition, we leverage our efficient, scalable operating model and integrated capabilities across our global infrastructure to effectively reach patients around the world.

At the 40th Annual J.P. Morgan Healthcare Conference in January 2022, we announced our Vision 2025, which aims to deliver sustainable growth and enhanced value, driving our continued transformation to an innovative, high-growth global pharmaceutical leader. The three core components of our Vision 2025 focus on commercial execution, pipeline productivity and operational excellence.

Our lead marketed products are:

Neuroscience

- **Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution**, a product approved by the U.S. Food and Drug Administration, or FDA, in July 2020 and launched in the U.S. in November 2020 for the treatment of cataplexy or excessive daytime sleepiness, or EDS, in patients with narcolepsy aged seven years of age and older, and also approved by FDA in August 2021 for the treatment of idiopathic hypersomnia, or IH, in adults and launched in the U.S. in November 2021. Xywav contains 92% less sodium than Xyrem®;

- **Xyrem (sodium oxybate) oral solution**, a product approved by FDA and distributed in the U.S. for the treatment of both cataplexy and EDS in patients seven years of age and older with narcolepsy; Jazz also markets Xyrem in Canada for the treatment of cataplexy in patients with narcolepsy. Xyrem is also approved and distributed in Europe, Great Britain and other markets through a licensing agreement;
- **Epidiolex® (cannabidiol) oral solution**, a product approved by FDA and launched in the U.S. in 2018 by GW Pharmaceuticals plc, or GW, and currently indicated for the treatments of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex (TSC) in patients one year of age or older; in Europe (where it is marketed as Epidyolex®) and other markets, it is approved for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome, in conjunction with clobazam (EU and Great Britain only), in patients 2 years of age and older and for adjunctive treatment of seizures associated with TSC in patients 2 years of age and older;
- **Sunosi® (solriamfetol)**, a product approved by FDA and marketed in the U.S., Canada, Europe and Great Britain to improve wakefulness in adult patients with EDS associated with narcolepsy or obstructive sleep apnea, or OSA; and
- **Sativex® (nabiximols) oral solution**, a product approved and marketed in the U.K., Canada and other markets as treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis, or MS, who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy.

Oncology

- **Zepzelca® (lurbinectedin)**, a product approved by FDA in June 2020 and launched in the U.S. in July 2020 for the treatment of adult patients with metastatic small cell lung cancer, or SCLC, with disease progression on or after platinum-based chemotherapy; in Canada, Zepzelca was approved in September 2021 for the treatment of adults with Stage III or metastatic SCLC, who have progressed on or after platinum-containing therapy;
- **Rylaze™** (recombinant Erwinia asparaginase), a product approved by FDA in June 2021 and launched in the U.S. in July 2021 for use as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia, or ALL, or lymphoblastic lymphoma, or LBL, in adults and pediatric patients who have developed hypersensitivity to *E. coli*-derived asparaginase;
- **Vyxeos® (daunorubicin and cytarabine) liposome for injection**, a product approved in the U.S., Canada, Europe and Great Britain (marketed as Vyxeos® liposomal in Europe and Great Britain) for the treatment of adults with newly-diagnosed therapy-related acute myeloid leukemia, or t-AML, or AML with myelodysplasia-related changes (AML-MRC). An expanded indication was granted in the U.S. for the treatment of newly diagnosed t-AML or AML-MRC in pediatric patients aged 1 year and older; and
- **Defitelio® (defibrotide sodium)** is a product approved in the U.S. and Brazil for the treatment of hepatic veno-occlusive disease, or VOD, with renal or pulmonary dysfunction following hematopoietic stem cell transplantation, or HSCT, and in Japan for the treatment of hepatic sinusoidal obstruction syndrome (hepatic-veno occlusive disease). It is currently approved in the EU, Great Britain, Canada, Israel, South Korea, Australia and Switzerland for the treatment of severe hepatic VOD, also known as sinusoidal obstructive syndrome, or SOS, in HSCT therapy. It is indicated in adults and pediatric patients over 1 month of age.

Our strategy to deliver sustainable growth and enhanced value is focused on:

- Strong commercial execution to drive diversified revenue growth and address unmet medical needs of our patients across our product portfolio, which focuses on neuroscience and oncology medicines;
- Expanding and advancing our pipeline to achieve a valuable product portfolio of durable, highly differentiated programs;
- Continuing to build a flexible, efficient and productive development engine for targeted therapeutic areas to identify and progress early-, mid- and late-stage assets;
- Identifying and acquiring novel product candidates and approved therapies to complement our existing pipeline and commercial portfolio;
- Investing in an efficient, scalable operating model and differentiated capabilities to enable growth; and
- Unlocking further value through indication expansion and entry into global markets.

In 2021, consistent with our strategy, we continued to focus on research and development activities within our neuroscience and oncology therapeutic areas. For a summary of our ongoing research and development activities, see “Business—Research and Development” in Part I, Item 1 of this Annual Report on Form 10-K.

Research and Development Progress

Our development activities encompass all stages of development and currently include clinical testing of new product candidates and activities related to clinical improvements of, or additional indications or new clinical data for, our existing marketed products. We also have active preclinical programs for novel therapies, including precision medicines in hematology and oncology and the GW cannabinoid platform. We are increasingly leveraging our growing internal research and development function, and we have also entered into collaborations with third parties for the research and development of innovative early-stage product candidates and have supported additional investigator-sponsored trials, or ISTs, that are anticipated to generate additional data related to our products. We also seek out investment opportunities in support of development of early- and mid-stage technologies in our therapeutic areas and adjacencies. We have a number of licensing and collaboration agreements with third parties, including biotechnology companies, academic institutions and research-based companies and institutions, related to preclinical and clinical research and development activities in hematology and in precision oncology, as well as in neuroscience.

With the approvals and launches of Rylaze for the treatment ALL or LBL in pediatric and adult patients one month and older who have developed hypersensitivity to *E. coli*-derived asparaginase and Xywav for IH in 2021, we accomplished our goal to deliver five product launches through 2020 and 2021. We have taken both Rylaze and Xywav from concept to commercialization.

Our neuroscience R&D efforts include the planned initiation of a pivotal Phase 3 clinical trial of Epidiolex for the treatment of Epilepsy with Myoclonic-Atonic Seizures, or EMAS, also known as Doose syndrome, in the first half of 2022. This trial is expected to evaluate Epidiolex in a fourth childhood-onset epileptic encephalopathy with high unmet need. EMAS is characterized by generalized myoclonic-atonic seizures, and this trial is designed to provide the first randomized, controlled clinical data with Epidiolex in this syndrome type. Seizure types including atonic, tonic, clonic, tonic-clonic, and partial onset seizures are seen in Lennox-Gastaut syndrome, or LGS, Dravet syndrome, or DS, and tuberous sclerosis complex, or TSC.

For nabiximols, we have three ongoing Phase 3 clinical trials in multiple sclerosis (MS)-related spasticity. Spasticity occurs in up to 84% of MS patients, and approximately one-third of those who experience spasticity live with uncontrolled symptoms. The first trial is a smaller, shorter trial relative to the other two. If results from this first trial are positive, there is the potential for a New Drug Application, or NDA, submission in the U.S. by the end of 2022.

Additionally, in December 2021 we initiated Phase 2 clinical trials for suvecaltamide (JZP385) for essential tremor, or ET, and for JZP150 for post-traumatic stress disorder, or PTSD. These are both patient populations that suffer significant impacts to their quality of life and for whom there are limited current treatment options. We are also pursuing early-stage activities related to the development of JZP324, an extended-release low sodium, oxybate formulation that we believe could provide a clinically meaningful option for narcolepsy patients.

Within our oncology R&D program, there is a robust development plan being executed for Zepzelca. We are collaborating with Roche on a pivotal Phase 3 clinical trial evaluating Zepzelca in combination with Tecentriq in first-line extensive stage SCLC. In December 2021, our licensor PharmaMar initiated a confirmatory trial in second-line SCLC. This is expected to be a three-arm trial comparing Zepzelca as either monotherapy or in combination with irinotecan to investigator's choice of irinotecan or topotecan. Data from this trial, if positive, could confirm the benefit of Zepzelca in the treatment of SCLC when patients progress following first-line treatment with a platinum-based regimen.

In 2022 we initiated a Phase 2 basket trial to explore Zepzelca monotherapy in patients with select advanced or metastatic solid tumors. Cohorts will include advanced urothelial cancer, large cell neuroendocrine tumor of the lung, and homologous recombinant deficient positive (HRD+) cancers. In addition, we have initiated a Phase 4 observational study to collect real world safety and outcome data in adult Zepzelca monotherapy patients with SCLC who progress on or after prior platinum-containing chemotherapy.

For Rylaze, in January 2022 we submitted a sBLA with data in support of a Monday/Wednesday/Friday (M/W/F) IM dosing schedule, which has been granted review under the Real-Time Oncology Review, or RTOR, program. Part two of the ongoing Rylaze study is evaluating intravenous administration. We are planning regulatory submissions in Europe in mid-2022.

A summary of our key ongoing and planned development projects is provided under “Business—Research and Development” in Part I, Item 1 of this Annual Report on Form 10-K.

2021 Highlights and Recent Developments

Regulatory Submissions, Approvals and Commercial Launches

Oxybate Franchise

- In June 2021, FDA recognized seven years of Orphan Drug Exclusivity (ODE) for Xywav in narcolepsy through July 21, 2027.
- In August 2021, FDA approved our sNDA for Xywav for the treatment of IH in adults and in November 2021, we commenced the U.S. commercial launch.
- In January 2022, FDA recognized seven years of ODE for Xywav in IH through August 12, 2028.

Epidiolex/Epidyolex

- In 2021, the U.K. Medicines and Healthcare Products Regulatory Agency (MHRA), as well as the EU, approved a new indication for Epidyolex as an adjunctive treatment of seizures associated with TSC, for patients two years of age and older.

Sunosi

- In May 2021, Sunosi was approved in Canada for the treatment of EDS associated with narcolepsy or OSA in adult patients.

Zepzelca

- In September 2021, Zepzelca received conditional approval in Canada for the treatment of adult patients with Stage III or metastatic SCLC who have progressed on or after platinum-containing therapy. In November 2021, Zepzelca was made commercially available in Canada.

Rylaze

- In June 2021, Rylaze was approved by FDA under the Real-Time Oncology Review, or RTOR, program for use as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL or LBL in pediatric and adult patients one month and older who have developed hypersensitivity to *E. coli*-derived asparaginase. In July 2021, we launched Rylaze in the U.S.
- In January 2022, we submitted a sBLA for Rylaze with additional data in support of a Monday/Wednesday/Friday (M/W/F) IM dosing schedule, which has been granted review under the RTOR program.

Vyxeos

- In March 2021, FDA approved a revised label for Vyxeos to include a new indication to treat newly-diagnosed t-AML or AML with myelodysplasia-related changes in pediatric patients aged one year and older.

Research & Development

- In December 2021, we initiated a Phase 2 clinical trial for suvecaltamide (JZP385) for ET.
- In December 2021, we initiated a Phase 2 trial for JZP150 for PTSD.
- In December 2021, in collaboration with Roche, we have initiated a Phase 3 pivotal clinical trial in first-line extensive stage SCLC of Zepzelca in combination with Tecentriq® (atezolizumab).

Other Significant Developments

- In May 2021, we acquired GW. The total consideration paid by us for the entire issued share capital of GW was $7.2 billion. The GW Acquisition, closed on May 5, 2021. As a result, GW became an indirect wholly owned subsidiary of the Company.
- In connection with the financing of the transaction, in April 2021, we closed an offering of $1.5 billion in aggregate principal amount of 4.375% senior secured notes, due 2029, or the Secured Notes. In May 2021, we entered into a credit agreement, or the Credit Agreement, that provides for (i) a seven-year $3.1 billion term loan B facility, or the Dollar Term Loan, (ii) a seven-year €625.0 million term loan B facility, or the Euro Term Loan and, together with the Dollar Term Loan, collectively known as the Term Loan and (iii) a five-year $500.0 million revolving credit facility, or the Revolving Credit Facility. We financed the cash portion of the GW Acquisition consideration through a combination of cash on hand and borrowings under the Term Loan and the Secured Notes. The Revolving Credit Facility is currently undrawn.

Acquisition of GW Pharmaceuticals Plc

In May 2021, we acquired GW with the objectives of broadening our neuroscience portfolio, further diversifying our revenue and driving sustainable, long-term value creation opportunities. The total consideration paid by us for the entire issued share capital of GW was $7.2 billion.

GW's lead product, Epidiolex (cannabidiol) oral solution, is approved in patients one-year and older for the treatment of seizures associated with LGS, DS and TSC, all of which are rare diseases characterized by severe early-onset epilepsy. Epidiolex was the first plant-derived cannabinoid medicine ever approved by FDA, and has also been approved in Europe under the trade name Epidyolex. In addition to the approved indications for Epidiolex, we believe there are considerable opportunities to pursue other indications within the epilepsy field, including other treatment-resistant epilepsies where significant unmet needs of patients exist. We plan to initiate a pivotal Phase 3 clinical trial of Epidiolex for the treatment of seizures associated with EMAS, known as Doose syndrome, in the first half of 2022. EMAS represents the fourth target indication for Epidiolex.

We plan to continue to leverage the GW cannabinoid platform and significant expertise in discovering, developing, manufacturing and commercializing therapeutics to address a broad range of diseases. This platform includes nabiximols, which is in Phase 3 clinical trials for the treatment of spasticity associated with multiple sclerosis with an additional planned Phase 3 clinical trial in spasticity associated with spinal cord injury, as well as earlier-stage cannabinoid product candidates.

We view the GW Acquisition as consistent with our overall business and capital allocation strategy to expand our neuroscience portfolio and drive substantial value for our shareholders.

Operational Excellence

We remain focused on continuing to build excellence in areas that we believe will give us a competitive advantage, including building an increasingly agile and adaptable commercialization engine and strengthening our customer-focused market expertise across patients, providers and payors. We are refining our approach to engaging our customers by strengthening alignment and integration across functions and across regions. This includes a more integrated approach to brand planning, a heightened focus on launch and operational excellence and multichannel customer engagement. We have fully adapted to virtual scientific congresses designed to ensure we can continue to provide promotional and non-promotional interactions and have supported our field-based teams with virtual customer interaction tools, training and content. These initiatives mark a significant operational evolution that is directly linked to our corporate strategy and are designed to better enable our teams to work collaboratively on an aligned and shared agenda through both virtual and in-person interactions. We anticipate that our teams will increase the frequency of in-person interactions as medical congresses and healthcare practices begin to resume in-person activities, taking into account applicable public health authority and local government guidelines which are designed to ensure community and employee safety.

COVID-19 Business Update

We have implemented a comprehensive response strategy designed to manage the impact of the COVID-19 pandemic on our employees, patients and our business. The prolonged nature of the pandemic is negatively impacting our business in a varied manner due to the emergence of the Delta and Omicron variants and other variants with increased transmissibility, even in some cases in vaccinated people, including limited access to health care provider offices and institutions and the willingness of patients or parents of patients to seek treatment or change existing treatments. We expect that our business, financial condition, results of operations and growth prospects may continue to be negatively impacted by the pandemic on a limited basis that may vary depending on the context. However we have begun to observe, and expect to continue to observe, a gradual normalization in patient and healthcare provider practices, as providers and patients have adapted their behaviors and procedures to the evolving circumstances and as COVID-19 vaccines continue to be administered.

Workplace and Employees

We support broad public health strategies designed to prevent the spread of COVID-19 and are focused on the health and welfare of our employees. Our global organization has mobilized to enable our employees to accomplish our most critical goals through a combination of remote work and in-person initiatives. In addition to rolling out new technologies and collaboration tools, we have implemented processes and resources to support our employees in the event an employee receives a positive COVID-19 diagnosis. We have developed plans regarding the opening of our sites to enable our employees to return to work in our global offices, the field and our manufacturing facilities, which take into account applicable public health authority and local government guidelines and which are designed to ensure community and employee safety. We are moving to a more flexible mix of virtual and in-person working to advance our culture, drive innovation and agility and enable greater balance and well-being for our workforce. This will also enable us to reconfigure our physical workspaces to optimize the footprint of our company-owned or leased office spaces.

Commercialization

There continues to be some negative impact on demand, new patient starts and treatments for our products arising from the pandemic, primarily due to the inherent limitations of telemedicine and a reprioritization of healthcare resources toward COVID-19. As healthcare systems have adapted to cope with the ongoing situation, we have seen improvements. We are utilizing technology to continue to engage healthcare professionals and other customers virtually to support patient care. As more clinics and institutions begin to allow in-person interactions pursuant to local health authority and government guidelines, our field teams continue to resume in-person interactions with healthcare professionals and clinics combined with virtual engagement. The level of renewed in-person engagement varies by account, region and country and may be adversely impacted in the future as a result of the continuing impact of the COVID-19 pandemic. The lack of access to health care providers has caused, and may continue to cause, delays in appropriate diagnosis, treatment and ongoing care for some patients, which has negatively impacted, and could continue to impact, prescribing and use of our products.

Supply Chain

Our manufacturing facilities in Athlone, Ireland, which produces Xywav and Xyrem, Villa Guardia, Italy, which produces defibrotide, and Kent Science Park, U.K., which produces Epidiolex/Epidyolex and Sativex, are operational with essential staff onsite and office-based staff working onsite and remotely as business needs require. We currently expect to have adequate global supply of all products for 2022.

Research and Development

With respect to our clinical trial activities, we have taken measures to implement remote and virtual approaches, including remote data monitoring where possible, to maintain patient safety and trial continuity and to preserve study integrity. We have seen limited COVID-19-related impact to our mid- and late-stage clinical trial activity, despite delays in initiating trial sites. We rely on contract research organizations or other third parties to assist us with clinical trials, and we cannot guarantee that they will continue to perform their contractual duties in a timely and satisfactory manner as a result of the evolving effects of the COVID-19 pandemic. Similarly, our ability to recruit and retain patients and principal investigators and site staff who, as health care providers, may have heightened exposure to COVID-19, may adversely impact our clinical trial operations. Supply chain disruptions related to the pandemic may also impact our ability to initiate clinical trials in a timely manner.

Corporate Response

The COVID-19 pandemic has caused a significant burden on health systems globally and has highlighted the need for companies to evaluate existing therapies to assess if they can be utilized beyond their current indications to treat COVID-19 as well as consider developing new therapies. To this end, we have granted requests for several ISTs to evaluate the use of defibrotide in COVID-19 patients experiencing respiratory distress.

In addition, we are supporting our local communities and patient-focused organizations in COVID-19 relief efforts including through corporate donations to charitable organizations providing food and medical relief to communities in which we operate, and other localities where the needs related to the impact of COVID-19 are greatest. We are engaging with patient advocacy organizations to better understand the impact of COVID-19 and working to enable patients living with sleep disorders, epilepsies and oncology conditions with access to treatments and that their other needs are addressed given the impact of COVID-19 on the healthcare system. We are committed to enabling our employees to give back, including allowing licensed healthcare practitioners employed by us to support local response efforts.

Other Challenges, Risks and Trends Related to Our Business

Our business has been substantially dependent on Xyrem. Our future plans assume that our newly launched oxybate product Xywav, with 92% lower sodium compared to Xyrem, depending on the dose, absence of a sodium warning and dosing titration option, will become the treatment of choice for patients who can benefit from oxybate treatment, current Xyrem patients, and patients who previously were not prescribed Xyrem, including those patients for whom sodium content is a concern. In June 2021, FDA recognized seven years of ODE for Xywav in narcolepsy through July 21, 2027 stating that Xywav is clinically superior to Xyrem by means of greater safety due to reduced chronic sodium burden. While we expect that our business will continue to be substantially dependent on oxybate product sales from both Xywav and Xyrem, there is no guarantee that we can maintain oxybate sales at or near historical levels, or that oxybate sales will continue to grow.

Our ability to successfully commercialize Xywav will depend on, among other things, our ability to maintain adequate coverage and reimbursement for Xywav and acceptance of Xywav by payors, physicians and patients, including of Xywav for the treatment of idiopathic hypersomnia in adults. In an effort to support strong adoption of Xywav, we are focused on providing robust patient copay and savings programs and facilitating payor coverage for Xywav. Moreover, we have increasingly experienced pressure from third party payors to agree to discounts, rebates or restrictive pricing terms, and we cannot guarantee we will be able to agree to commercially reasonable terms with pharmacy benefit managers, or PBMs, and

other third party payors, or that we will be able to ensure patient access and acceptance on institutional formularies. Entering into agreements with PBMs and payors to ensure patient access has and will likely continue to result in higher gross to net deductions. In addition to the COVID-19 related impacts described above, in the future, we expect our oxybate products to face competition from generic and authorized generic versions of sodium oxybate pursuant to the settlement agreements we have entered into with multiple abbreviated new drug application, or ANDA, filers. Generic competition can decrease the prices at which Xywav and Xyrem are sold and the number of prescriptions written for Xywav and Xyrem. Xywav and Xyrem may also face increased competition from new branded products for treatment of cataplexy and/or EDS in narcolepsy in the U.S. market.

Our financial condition, results of operations and growth prospects are also dependent on our ability to maintain or increase sales of Epidiolex/Epidyolex in the U.S. and Europe, which is subject to many risks and there is no guarantee that we will be able to continue to successfully commercialize Epidiolex for its approved indications. While we have established our Epidiolex commercial team and have hired our U.S. and European sales forces, we will need to continue to maintain and further develop the teams to continue to successfully coordinate the commercialization of Epidiolex. The commercial success of Epidiolex depends on the extent to which patients and physicians accept and adopt Epidiolex as a treatment for seizures associated with LGS, DS and TSC, and we do not know whether our or others' estimates in this regard will be accurate. Physicians may not prescribe Epidiolex and patients may be unwilling to use Epidiolex if coverage is not provided or reimbursement is inadequate to cover a significant portion of the cost. Additionally, any negative development for Epidiolex in the market after launch, in clinical development for additional indications, or in regulatory processes in other jurisdictions, may adversely impact the commercial results and potential of Epidiolex. Thus, significant uncertainty remains regarding the commercial potential of Epidiolex.

In addition to our neuroscience products and product candidates, we are commercializing a portfolio of oncology products, including Defitelio, Vyxeos, Rylaze and Zepzelca. An inability to effectively commercialize Defitelio, Vyxeos, Rylaze and Zepzelca and to maximize their potential where possible through successful research and development activities could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

A key aspect of our growth strategy is our continued investment in our evolving and expanding research and development activities. If we are not successful in the clinical development of these or other product candidates, if we are unable to obtain regulatory approval for our product candidates in a timely manner, or at all, or if sales of an approved product do not reach the levels we expect, our anticipated revenue from our product candidates would be negatively affected, which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

In addition to continued investment in our research and development pipeline, we intend to continue to grow our business by acquiring or in-licensing, and developing, including with collaboration partners, additional products and product candidates that we believe are highly differentiated and have significant commercial potential. Failure to identify and acquire, in-license or develop additional products or product candidates, successfully manage the risks associated with integrating any products or product candidates into our portfolio or the risks arising from anticipated and unanticipated problems in connection with an acquisition or in-licensing, such as the GW Acquisition, could have a material adverse effect on our business, results of operations and financial condition.

The success of the GW Acquisition will depend, in part, on our ability to realize the anticipated benefits from successfully combining our and GW's businesses and we plan to continue to devote substantial management attention and resources to integrating our business practices and operations with GW's in an effort to fully realize the anticipated benefits of the GW Acquisition. Nonetheless, Epidiolex and the other products and technologies acquired may not be successful or continue to grow at the same rate as if our companies operated independently or they may require significantly greater resources and investments than originally anticipated. Conversely, the liabilities assumed in the GW Acquisition may be greater than originally anticipated. In addition, difficulties may arise during the process of combining the operations of our companies that could result in the failure to achieve the synergies or free cash flow that we anticipate, the failure to integrate operations and internal systems, programs and controls, the loss of key employees that may be difficult to replace in the very competitive pharmaceutical field, the failure to harmonize both companies' corporate cultures, and the disruption of each company's ongoing businesses or inconsistencies in standards, controls, procedures and policies that adversely affect our ability to maintain relationships with customers, suppliers, distributors, collaboration partners, clinical trial investigators or managers of our clinical trials. As a result, the anticipated benefits of the GW Acquisition may not be realized fully within the expected timeframe or at all or may take longer to realize or cost more than expected, which could materially and adversely affect our business, financial condition, results of operations and growth prospects.

Our industry has been, and is expected to continue to be, subject to healthcare cost containment and drug pricing scrutiny by regulatory agencies in the U.S. and internationally. If healthcare policies or reforms intended to curb healthcare costs are adopted or if we experience negative publicity with respect to pricing of our products or the pricing of pharmaceutical drugs generally, the prices that we charge for our products may be affected, our commercial opportunity may be limited and/or our revenues from sales of our products may be negatively impacted. We are also subject to increasing pricing pressure and restrictions on reimbursement imposed by payors. If we fail to obtain and maintain adequate formulary positions and

institutional access for our products and future approved products, we will not be able to achieve a return on our investment and our business, financial condition, results of operations and growth prospects would be materially adversely affected.

While certain preparations of cannabis remain Schedule I controlled substances, if such products are approved by FDA for medical use in the U.S. they are rescheduled to Schedules II-V, since approval by FDA satisfies the "accepted medical use" requirement; or may be removed from control under the Controlled Substances Act entirely. If any of our product candidates receive FDA approval, the U.S. Drug Enforcement Administration, or DEA, will make a scheduling determination. If any foreign regulatory authority determines that Epidyolex may have potential for abuse, or if DEA makes a similar determination for nabiximols, it may require us to generate more clinical or other data than we currently anticipate to establish whether or to what extent the substance has an abuse potential, which could increase the cost, delay the approval and/or delay the launch of that product. In addition, there are non-FDA approved cannabidiol preparations being made available from companies through the state-enabled medical marijuana industry, which might attempt to compete with Epidiolex and, if approved by FDA, nabiximols. If we are unable to compete successfully, our commercial opportunities will be reduced and our business, results of operations and financial conditions may be materially harmed.

Finally, business practices by pharmaceutical companies, including product formulation improvements, patent litigation settlements, and risk evaluation and mitigation strategy, or REMS, programs, have increasingly drawn public scrutiny from legislators and regulatory agencies, with allegations that such programs are used as a means of improperly blocking or delaying competition. If we become the subject of any future government investigation with respect to our business practices, including as they relate to the Xywav and Xyrem REMS, the launch of Xywav, our Xyrem patent litigation settlement agreements or otherwise, we could incur significant expense and could be distracted from operation of our business and execution of our strategy. From June 2020 to October 2021, a number of lawsuits were filed on behalf of purported direct and indirect Xyrem purchasers, alleging that the patent litigation settlement agreements we entered with certain generic companies violate state and federal antitrust and consumer protection laws. For additional information on these lawsuits, see Note 14, Commitments and Contingencies-Legal Proceedings of the Notes to Consolidated Financial Statements, included in Part IV of this Annual Report on Form 10-K. It is possible that additional lawsuits will be filed against us making similar or related allegations. We cannot predict the outcome of these or potential additional lawsuits or government action; however, if the plaintiffs were to be successful in their claims, they may be entitled to injunctive relief or we may be required to pay significant monetary damages. Any of the foregoing risks and uncertainties could have a material adverse effect on our business, financial condition, results of operations and growth prospects. In addition, to the extent the COVID-19 pandemic continues to adversely affect our business and results of operations, it may also have the effect of heightening many of the other risks and uncertainties described above. All of these risks and uncertainties are discussed in greater detail, along with other risks and uncertainties, in "Risk Factors" in Part I, Item 1A of this Annual Report on Form 10-K.

Results of Operations

The following table presents revenues and expenses for the years ended December 31, 2021, 2020 and 2019 (in thousands except percentages):

	2021(1)	Change	2020	Change	2019
Product sales, net	$ 3,079,001	31 %	$ 2,346,660	10 %	$ 2,135,601
Royalties and contract revenues	15,237	(10)%	16,907	(35)%	26,160
Cost of product sales (excluding amortization of acquired developed technologies)	440,760	196 %	148,917	16 %	127,930
Selling, general and administrative	1,451,683	70 %	854,233	16 %	736,942
Research and development	505,748	51 %	335,375	12 %	299,726
Intangible asset amortization	525,769	103 %	259,580	(27)%	354,814
Impairment charge	—	N/A(2)	136,139	N/A(2)	—
Acquired in-process research and development	—	N/A(2)	251,250	N/A(2)	109,975
Interest expense, net	278,766	180 %	99,707	38 %	72,261
Foreign exchange loss	4,350	33 %	3,271	(44)%	5,811
Income tax expense (benefit)	216,116	545 %	33,517	N/A(2)	(73,154)
Equity in loss of investees	714	(76)%	2,962	(28)%	4,089

(1) The results of operations of the GW business have been included from the closing of the GW Acquisition on May 5, 2021.
(2) Comparison to prior period is not meaningful.

Revenues

The following table presents product sales, royalties and contract revenues, and total revenues for the years ended December 31, 2021, 2020 and 2019 (in thousands except percentages):

	2021	Change	2020	Change	2019
Xyrem	$ 1,265,830	(27)%	$ 1,741,758	6 %	$ 1,642,525
Xywav	535,297	N/A(1)	15,264	N/A(1)	—
Total Oxybate	1,801,127	3 %	1,757,022	7 %	1,642,525
Epidiolex/Epidyolex	463,645	N/A(2)	—	N/A(2)	—
Sunosi	57,914	104 %	28,333	N/A(1)	3,714
Sativex	12,707	N/A(2)	—	N/A(2)	—
Total Neuroscience	2,335,393	31 %	1,785,355	8 %	1,646,239
Zepzelca	246,808	173 %	90,380	N/A(1)	—
Rylaze	85,629	N/A(1)	—	N/A(1)	—
Vyxeos	134,060	11 %	121,105	— %	121,407
Defitelio/defibrotide	197,931	1 %	195,842	13 %	172,938
Erwinaze/Erwinase	69,382	(53)%	147,136	(17)%	177,465
Total Oncology	733,810	32 %	554,463	18 %	471,810
Other	9,798	43 %	6,842	(61)%	17,552
Product sales, net	3,079,001	31 %	2,346,660	10 %	2,135,601
Royalties and contract revenues	15,237	(10)%	16,907	(35)%	26,160
Total revenues	$ 3,094,238	31 %	$ 2,363,567	9 %	$ 2,161,761

(1) Comparison to prior period is not meaningful.
(2) The results of operations of the GW business have been included from the closing of the GW Acquisition on May 5, 2021 and comparison to prior period is not meaningful.

Product Sales, Net

Total oxybate product sales increased in 2021 compared to 2020 primarily due to a higher average selling price, partially offset by higher gross to net deductions driven by higher Tricare rebates and additional commercial payor contracts, and to a lesser extent a decrease in commercial sales volumes. Total oxybate revenue bottle volume decreased by 1% in 2021 compared to 2020 reflecting our continued investment in patient access programs during the launch of Xywav. Average active oxybate patients on therapy were approximately 16,200 in the fourth quarter of 2021, an increase of approximately 6% compared to the same period in 2020. Xyrem product sales decreased in 2021 compared to 2020 primarily due to a decrease in sales volume, due to the strong adoption of Xywav by existing Xyrem patients, partially offset by a higher average net selling price. Price increases were instituted in January 2021 and January 2020. Xywav product sales were $535.3 million in 2021 compared to $15.3 million in 2020, following its U.S. launch in November 2020. Total oxybate product sales increased in 2020 compared to 2019 primarily due to a higher average selling price and, to a lesser extent, an increase in commercial sales volume, partially offset by higher gross to net deductions. Total oxybate revenue bottle volume increased by 4% in 2020 compared to 2019 primarily driven by persistence and compliance among existing Xyrem patients. Xyrem product sales increased in 2020 compared to 2019 primarily due to a higher average selling price and, to a lesser extent, an increase in sales volume, partially offset by higher gross to net deductions driven by managed care plans and commercial payor contracts. Price increases were instituted in January 2020, and in January and July 2019. In 2020 new patient diagnoses and enrollments were negatively impacted by COVID-19. Epidiolex/Epidyolex product sales in 2021, from the closing of the GW Acquisition on May 5, 2021 to December 31, 2021 were $463.6 million. On a pro forma basis, Epidiolex/Epidyolex product sales increased by 29% in 2021 compared to 2020, primarily due to an increase in commercial sales volumes. Sunosi product sales increased in 2021, compared to 2020 primarily due to an increase in sales volume, partially offset by higher gross to net deductions. Sunosi product sales increased in 2020 compared to 2019 following launch in the U.S. in July 2019 and the European rolling launch commenced in May 2020.

Zepzelca product sales increased in 2021 compared to 2020 primarily due to higher sales volumes following launch in the U.S in July 2020. Rylaze product sales were $85.6 million in 2021, following its U.S. launch in July 2021. Vyxeos product sales increased in 2021 compared to 2020 primarily due to lower gross to net deductions driven by a reduction in the returns provision due to lower than estimated actual returns. Vyxeos product sales in 2020 were in line with 2019. Defitelio/defibrotide product sales increased in 2021 compared to 2020, primarily due to the positive impact of foreign exchange rates, partially offset by lower average net selling price due to regional mix. Defitelio/defibrotide product sales increased in 2020

compared to 2019, primarily due to higher sales volumes, partially offset by lower average net selling price due to regional mix. We distributed our final Erwinaze inventory in June 2021 following expiration of our license and supply agreement. Erwinaze/Erwinase product sales decreased in 2020 compared to 2019 primarily due to limited availability of supply of inventory from the manufacturer. We expect product sales, net will increase in 2022 over 2021, primarily due to an increase in sales of Xywav partially offset by a decrease in sales of Xyrem as patients continue to transition to Xywav, expected growth in, and the inclusion of a full year sales of, Epidiolex and Rylaze and expected growth in sales of Zepzelca.

Royalties and Contract Revenues

Royalties and contract revenues decreased in 2021 compared to 2020 primarily due to lower contract revenues from out-licensing agreements. Royalties and contract revenues decreased in 2020 compared to 2019 primarily due to lower milestone revenues from out-licensing agreements. We expect royalties and contract revenues to increase in 2022 compared to 2021 primarily due to increased royalty revenue.

Cost of Product Sales

Cost of product sales increased in 2021 compared to 2020, primarily due to the cost of product sales acquired in the GW Acquisition, including the acquisition accounting inventory fair value step-up expense, or fair value step-up expense. Cost of product sales increased in 2020 compared to 2019, primarily due to a change in product mix and an increase in net product sales. Gross margin as a percentage of net product sales was 85.7%, 93.7% and 94.0% in 2021, 2020 and 2019, respectively. The decrease in our gross margin percentage in 2021 compared to 2020 was primarily due to the impact of the fair value step-up expense. We expect our cost of product sales to increase in 2022 compared to 2021 primarily driven by the inclusion of a full year of fair value step-up expense.

Selling, General and Administrative Expenses

Selling, general and administrative expenses increased in 2021 compared to 2020 primarily due to transaction and integration-related expenses of $229.0 million in 2021, an increase in compensation-related expenses driven by higher headcount as a result of the GW Acquisition and increased investment in sales and marketing spend primarily related to Sunosi, Epidiolex and Xywav. Selling, general and administrative expenses increased in 2020 compared to 2019 primarily due to increased investment in sales, marketing and launch activities related to the launches of Zepzelca and Xywav in the U.S., and the continuation of the launch of Sunosi in the U.S., as well as an increase in other expenses related to the expansion of our business. We expect selling, general and administrative expenses in 2022 to decrease compared to 2021, primarily due to a reduction in transaction and integration-related expenses, together with synergies expected to be realized connected to the GW Acquisition, partially offset by the inclusion of full year expense related to the GW Acquisition.

Research and Development Expenses

Research and development expenses consist primarily of costs related to clinical studies and outside services, personnel expenses, milestone expenses and other research and development costs. Clinical study and outside services costs relate primarily to services performed by clinical research organizations, materials and supplies, and other third party fees. Personnel expenses relate primarily to salaries, benefits and share-based compensation. Other research and development expenses primarily include overhead allocations consisting of various support and facilities-related costs. We do not track fully-burdened research and development expenses on a project-by-project basis. We manage our research and development expenses by identifying the research and development activities that we anticipate will be performed during a given period and then prioritizing efforts based on our assessment of which development activities are important to our business and have a reasonable probability of success, and by dynamically allocating resources accordingly. We also continually review our development pipeline projects and the status of their development and, as necessary, reallocate resources among our development pipeline projects that we believe will best support the future growth of our business.

The following table provides a breakout of our research and development expenses by major categories of expense (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Clinical studies and outside services	$ 234,462	$ 169,904	$ 133,042
Personnel expenses	193,716	127,794	100,090
Milestone expense	15,000	1,000	26,000
Other	62,570	36,677	40,594
Total	$ 505,748	$ 335,375	$ 299,726

Research and development expenses increased by $170.4 million in 2021 compared to 2020. Clinical studies and outside services costs increased in 2021 compared to 2020 primarily due to the addition of costs related to clinical programs for

nabiximols, Epidiolex and cannabinoids and an increase in costs related to suvecaltamide (JZP385) and JZP150. Personnel expenses increased by $65.9 million in 2021 compared to 2020, primarily due to increased headcount primarily driven by the GW Acquisition. Milestone expense of $15.0 million in 2021 primarily related to milestones expense of $13.0 million made under our asset purchase and collaboration agreements with Redx Pharma, or Redx. Research and development expenses increased by $35.6 million in 2020 compared to 2019. Clinical studies and outside services costs increased in 2020 compared to 2019 primarily due to the progress made on our clinical programs, including JZP458 and JZP385. Personnel expenses increased by $27.7 million in 2020 compared to 2019, primarily due to increased headcount in support of our development programs. Milestone expense of $26.0 million in 2019 related to milestone payments made under our license and option agreement with Ligand Pharmaceuticals Incorporated, or Ligand.

For 2022, we expect that our research and development expenses will continue to increase from previous levels due to the inclusion of a full year of expense with respect to the acquired GW business and as we prepare for anticipated data read-outs from clinical trials, initiate and undertake additional clinical trials and related development work and potentially acquire rights to additional product candidates.

Intangible Asset Amortization

Intangible asset amortization increased by $266.2 million in 2021 compared to 2020 primarily due to the commencement of amortization on the intangible assets arising from the GW Acquisition in May 2021, primarily related to Epidiolex. Intangible asset amortization decreased in 2020 compared to 2019 primarily due to the amortization of the cost of the priority review voucher, or PRV, of $111.1 million in full in 2019 following the notification to FDA of our intention to redeem it in the NDA submission for Xywav, partially offset by the commencement of amortization of the Zepzelca intangible asset upon FDA approval in June 2020. Intangible asset amortization is expected to increase in 2022 compared to 2021 primarily as a result of the inclusion of a full years amortization on the intangible assets acquired in the GW Acquisition.

Impairment Charges

In 2020, we recorded an acquired in-process research and development, or IPR&D, asset impairment charge of $136.1 million following the decision to stop enrollment in our Phase 3 clinical study of defibrotide for the prevention of VOD due to a determination that the study was highly unlikely to reach one of its primary endpoints.

Acquired In-Process Research and Development

Acquired IPR&D expense in 2020 primarily related to an upfront payment of $200.0 million to PharmaMar in connection with our license agreement for Zepzelca. In 2019, acquired IPR&D expense primarily related to an upfront payment of $56.0 million to Codiak in connection with our strategic collaboration agreement and the value attributed to suvecaltamide (JZP385) in the acquisition of Cavion, Inc., or Cavion.

Interest Expense, Net

Interest expense, net increased by $179.1 million in 2021 compared to 2020, primarily due to increased interest expense incurred on the Term Loan and the Secured Notes which were used, in part, to finance the cash portion of the GW Acquisition and higher non-cash interest expense following the issuance of our 2.00% exchangeable senior notes due 2026, or the 2026 Notes, in June 2020. Interest expense, net increased by $27.4 million in 2020 compared to 2019, primarily due to higher non-cash interest expense following the issuance of the 2026 Notes, lower interest income and a loss on extinguishment of debt related to the partial repurchases of our 1.875% exchangeable senior notes due 2021, or the 2021 Notes. We adopted ASU No. 2020-06, “Debt—Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging— Contracts in Entity’s Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity’s Own Equity”, or ASU 2020-06, on January 1, 2022, and as a result we expect interest expense, net to decrease in 2022 compared to 2021 due to decreased non-cash interest expense on our 1.50% exchangeable senior notes due 2024, or the 2024 Notes and the 2026 Notes, as we will no longer recognize non-cash interest expense on the debt discount, partially offset by an increase in interest expense primarily related to a full year of interest expense on the Term Loan and Secured Notes. For more information relating to ASU 2020-06 see Note 2, Summary of Significant Accounting Policies included in the Notes to Consolidated Financial Statements, included in Part IV of this Annual Report on Form 10-K.

Foreign Exchange Loss

The foreign exchange loss is primarily related to the translation of euro and sterling-denominated net monetary liabilities, primarily intercompany balances, held by subsidiaries with a U.S. dollar functional currency and related foreign exchange forward contracts not designated as hedging instruments.

Income Tax Expense (Benefit)

Our income tax expense was $216.1 million and $33.5 million in 2021 and 2020, respectively, and our income tax benefit was $73.2 million in 2019. Our income tax expense in 2021 included an expense of $259.9 million arising on the

remeasurement of our U.K. net deferred tax liability, which arose primarily in relation to the GW Acquisition, due to a change in the statutory tax rate in the U.K. following enactment of the U.K. Finance Act 2021. Excluding this impact, the increase in benefit for income taxes in 2021 compared to 2020 resulted primarily from the mix of pre-tax income and losses incurred across tax jurisdictions, deductions on subsidiary equity and the impacts recognized in 2020 of the disallowance of certain interest deductions and a provision for a proposed settlement reached with the French taxing authorities. Our income tax benefit in 2019 included a discrete tax benefit of $112.3 million resulting from an intra-entity intellectual property asset transfer. Excluding this effect, the increase in the effective tax rate for 2020 compared to 2019 was primarily due to the benefit recognized in 2019 from the application of the Italian patent box incentive regime 2015 through 2019 and the impacts recognized in 2020 of the disallowance of certain interest deductions and a provision for a proposed settlement reached with the French taxing authorities.

Equity in Loss of Investees

Equity in loss of investees relates to our share in the net loss of companies in which we have made investments accounted for under the equity method of accounting.

Liquidity and Capital Resources

As of December 31, 2021, we had cash and cash equivalents of $591.4 million, borrowing availability under our revolving credit facility of $500.0 million and a long-term debt principal balance of $6.4 billion. Our long-term debt included $3.3 billion aggregate principal amount Term Loan, $1.5 billion principal amount of the Secured Notes, $575.0 million principal amount of the 2024 Notes, and $1.0 billion principal amount of the 2026 Notes. During 2021, 2020 and 2019, we generated cash flows from operations of $778.5 million, $899.6 million and $776.4 million, respectively, and we expect to continue to generate positive cash flow from operations which will enable us to operate our business and de-lever our balance sheet over time.

In April 2021, we issued $1.5 billion in aggregate principal amount of the Secured Notes and in May 2021 we entered into the Credit Agreement that provides for $3.8 billion in aggregate principal amount of the Term Loan, and a five-year $500.0 million Revolving Credit Facility, which is currently undrawn. We used the proceeds from the Term Loan (i) to repay in full $575.9 million that was outstanding under our credit agreement, dated as of June 18, 2015, or the Existing Credit Agreement, (ii) to fund, in part, the cash consideration payable in connection with the GW Acquisition and (iii) to pay related fees and expenses. We expect to use future loans under the Revolving Credit Facility, if any, for general corporate purposes, including potential business development activities.

In September and December 2021, we made voluntary prepayments totaling €416.7 million or $502.0 million on the Euro Term Loan and in August 2021 we repurchased the remaining $218.8 million aggregate principal amount of our 1.875% exchangeable senior notes due 2021, or the 2021 Notes.

We have a significant amount of debt outstanding on a consolidated basis. For a more detailed description of our debt arrangements, including information relating to our scheduled maturities with respect to our long-term debt see Note 12, Debt, of the Notes to Consolidated Financial Statements, included in Part IV of this Annual Report on Form 10-K. This substantial level of debt could have important consequences to our business, including, but not limited to the factors set forth in in Part I, Item 1A “Risk Factors” of this Annual Report on Form 10-K under the heading “We have incurred substantial debt, which could impair our flexibility and access to capital and adversely affect our financial position, and our business would be adversely affected if we are unable to service our debt obligations.”

We believe that our existing cash and cash equivalents balance, cash we expect to generate from operations and funds available under our revolving credit facility will be sufficient to fund our operations and to meet our existing obligations for the foreseeable future. The adequacy of our cash resources depends on many assumptions, including primarily our assumptions with respect to product sales and expenses, as well as the other factors set forth in “Risk Factors” in Part I, Item 1A of this Annual Report on Form 10-K under the headings “Risks Related to our Lead Products and Product Candidates” and *“To continue to grow our business, we will need to commit substantial resources, which could result in future losses or otherwise limit our opportunities or affect our ability to operate and grow our business.”* Our assumptions may prove to be wrong or other factors may adversely affect our business, and as a result we could exhaust or significantly decrease our available cash resources, and we may not be able to generate sufficient cash to service our debt obligations which could, among other things, force us to raise additional funds and/or force us to reduce our expenses, either of which could have a material adverse effect on our business.

To continue to grow our business over the longer term, we plan to commit substantial resources to product acquisition and in-licensing, product development, clinical trials of product candidates and expansion of our commercial, development, manufacturing and other operations. In this regard, we have evaluated and expect to continue to evaluate a wide array of strategic transactions as part of our strategy to acquire or in-license and develop additional products and product candidates. Acquisition opportunities that we pursue could materially affect our liquidity and capital resources and may require us to incur

additional indebtedness, seek equity capital or both. We regularly evaluate the performance of our products and product candidates to ensure fit within our portfolio and support efficient allocation of capital. In addition, we may pursue new operations or continue the expansion of our existing operations. Accordingly, we expect to continue to opportunistically seek access to additional capital to license or acquire additional products, product candidates or companies to expand our operations or for general corporate purposes. Raising additional capital could be accomplished through one or more public or private debt or equity financings, collaborations or partnering arrangements. However, the COVID-19 pandemic continues to rapidly evolve and has resulted in significant volatility in the global financial markets. If this volatility persists and deepens, we could experience an inability to access additional capital or our liquidity could otherwise be impacted, which could in the future negatively affect our capacity for certain corporate development transactions or our ability to make other important, opportunistic investments. In addition, as a matter of Irish law, when an Irish public limited company issues ordinary shares to new shareholders for cash, the company must first offer those shares on the same or more favorable terms to existing shareholders on a pro rata basis, unless this statutory pre-emption obligation is dis-applied, or opted-out of, by approval of its shareholders. At our extraordinary general meeting of shareholders in September 2021, our shareholders voted to approve our proposal to dis-apply the statutory pre-emption obligation on terms that are substantially more limited than our general pre-emption opt-out authority that had been in effect prior to August 4, 2021, which could adversely affect our ability to effectively use our unissued share capital to fund in-licensing or acquisition opportunities, or to otherwise raise additional capital for our business. In any event, an inability to borrow or raise additional capital in a timely manner and on attractive terms could prevent us from expanding our business or taking advantage of acquisition opportunities, and could otherwise have a material adverse effect on our business and growth prospects. In addition, if we use a substantial amount of our funds to acquire or in-license products or product candidates, we may not have sufficient additional funds to conduct all of our operations in the manner we would otherwise choose. Furthermore, any equity financing would be dilutive to our shareholders, and could require the consent of the lenders under the Credit Agreement and the indenture for the Secured Notes for certain financings.

In November 2016, our board of directors authorized a share repurchase program and as of December 31, 2021 had authorized the repurchase of up to $1.5 billion, exclusive of any brokerage commissions. Under this program, which has no expiration date, we may repurchase ordinary shares from time to time on the open market. The timing and amount of repurchases will depend on a variety of factors, including the price of our ordinary shares, alternative investment opportunities, restrictions under the amended credit agreement, corporate and regulatory requirements and market conditions. The share repurchase program may be modified, suspended or discontinued at any time without prior notice. In 2021, we did not repurchase any of our ordinary shares under the share repurchase program. In 2020, we spent a total of $146.5 million to repurchase 1.2 million of our ordinary shares at an average total purchase price, including brokerage commissions, of $121.98 per share. All ordinary shares repurchased were canceled. As of December 31, 2021, the remaining amount authorized under the share repurchase program was $431.2 million.

The following table shows a summary of our cash flows for the periods indicated (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Net cash provided by operating activities	$ 778,507	$ 899,648	$ 776,401
Net cash used in investing activities	(5,212,143)	(1,007,670)	(155,300)
Net cash provided by (used in) financing activities	3,970,522	528,073	(293,745)
Effect of exchange rates on cash and cash equivalents	(3,207)	374	366
Net increase (decrease) in cash and cash equivalents	$ (466,321)	$ 420,425	$ 327,722

Operating activities

Net cash provided by operating activities decreased by $121.1 million in 2021 compared to 2020, primarily due to the payment of transaction and integration-related costs related to the GW Acquisition.

Net cash provided by operating activities increased by $123.2 million in 2020 compared to 2019, primarily due to a decrease in net outflow related to changes in operating assets and liabilities including the impact of the $58.6 million payment related to a civil settlement agreement with the DOJ and the OIG in 2019 together with an increase in accounts receivable of $38.6 million due to higher product sales together with the timing of receipts from customers and other working capital movements.

Investing activities

Net cash used in investing activities increased by $4,204.5 million in 2021 compared to 2020, primarily due to the following:

- $6,234.8 million outflow related to the net cash paid for the GW Acquisition; partially offset by
- $1,710.9 million increase in net proceeds from maturity of investments, primarily time deposits;
- $251.3 million decrease in upfront payments for acquired IPR&D primarily driven by the $200.0 million payment under our license agreement with PharmaMar and the $35.0 million payment under our asset purchase and exclusive license agreement with SpringWorks in 2020; and
- $95.1 million decrease in acquisition of intangible assets primarily related to our $100.0 million milestone payment to PharmaMar on FDA approval of Zepzelca in 2020.

Net cash used in investing activities increased by $852.4 million in 2020 compared to 2019, primarily due to the following:

- $710.6 million net increase in the acquisition of investments, primarily time deposits; and
- $189.6 million increase in upfront payments for acquired IPR&D primarily driven by our $200.0 million payment to PharmaMar and the $35.0 million to SpringWorks in 2020, compared to 2019 which included a payment of $56.0 million under our strategic collaboration agreement with Codiak; partially offset by
- The impact of consideration, net of cash acquired of $55.1 million related to our acquisition of Cavion in 2019.

Financing activities

Net cash provided by financing activities increased by $3,442.4 million in 2021 compared to 2020, primarily due to:

- An increase of $3,279.1 million in debt financing due to:
  - Net proceeds from issuance of borrowings under the Credit Agreement of $3,719.9 million and the Secured Notes of $1,471.5 million, partially offset by $1,101.8 million in repayment of long-term debt and payments for repurchase of the 2021 Notes of $218.8 million in the year ended December 31, 2021; compared to
  - Net proceeds from issuance of the 2026 Notes of $981.4 million, partially offset by payments for partial repurchase of the 2021 Notes of $356.2 million and repayment of long-term debt of $33.4 million in the year ended December 31, 2020.
- The impact of share repurchases of $146.5 million in the year ended December 31, 2020; and
- An increase of $35.6 million in proceeds from employee equity incentive and purchase plans in the year ended December 31, 2021.

Net cash provided by (used in) financing activities increased by $821.8 million in 2020 compared to 2019, primarily due to:

- The receipt of $981.4 million in net proceeds from the issuance of the 2026 Notes, partially offset by $356.2 million of payments for partial repurchases of the 2021 Notes;
- A decrease of $154.9 million in share repurchases; and
- An increase of $41.9 million in proceeds from employee equity incentive and purchase plans.

Credit Agreement

On May 5, 2021, the Company, Jazz Financing Lux S.à.r.l., or Jazz Lux, and certain of our other subsidiaries, as borrowers, (collectively with the Company and Jazz Lux, the "Borrowers"), entered into the Credit Agreement, that provides for (i) the Dollar Term Loan which was drawn by Jazz Lux on the Closing Date in U.S. dollars (ii) the Euro Term Loan which was drawn by Jazz Lux on the Closing Date in Euros and (iii) the Revolving Credit Facility, which is available to be drawn by any Borrower in U.S. dollars.

We used the proceeds from the Term Loan (i) to repay in full $575.9 million under the Existing Credit Agreement, (ii) to fund, in part, the cash consideration payable in connection with the GW Acquisition and (iii) to pay related fees and expenses. Upon the repayment in full of loans under the Existing Credit Agreement, it was terminated and all guarantees and liens thereunder were released.

Loans under the Term Loan and Revolving Credit Facility bear interest at a rate equal to (A) in the case of the Dollar Term Loan and the Revolving Credit Facility, at the applicable Borrower's option, either (a) London Inter-Bank Offered Rate, or LIBOR or (b) the prime lending rate and (B) in the case of the Euro Term Loan, Euro Inter-Bank Offered Rate, or EURIBOR, in each case, plus an applicable margin. The applicable margin for the Term Loan is 3.50% (in the case of LIBOR or EURIBOR borrowings) and 2.50% (in the case of borrowings at the prime lending rate). The applicable margin for the Revolving Credit Facility ranges from 3.25% to 2.75% (in the case of LIBOR borrowings) and 2.25% to 1.75% (in the case of borrowings at the prime lending rate), depending on our first lien secured net leverage ratio level. The Dollar Term Loan is subject to a LIBOR floor of 0.50%, the Euro Term Loan and loans under the Revolving Credit Facility are not subject to a EURIBOR or LIBOR (as applicable) floor. The Revolving Credit Facility has a commitment fee payable on the undrawn amount ranging from 0.50% to 0.40% per annum based upon our first lien secured net leverage ratio.

As of December 31, 2021, the interest rate and effective interest rate on the Dollar Term Loan were 4.00% and 4.55%, respectively. The interest rate and effective interest rate on the Euro Term Loan were 4.43% and 4.93%, respectively. As of December 31, 2021, we had an undrawn Revolving Credit Facility totaling $500.0 million.

The Borrowers' obligations under the Credit Agreement and any hedging or cash management obligations entered into with any lender thereunder are guaranteed by the Company, the other borrowers, and each of the Company's other existing or subsequently acquired or organized direct and indirect subsidiaries (subject to certain exceptions), or the Guarantors. We refer to the Borrowers and the Guarantors collectively as the "Loan Parties."

The Loan Parties' obligations under the Credit Agreement are secured, subject to customary permitted liens and other exceptions, by a security interest in (a) all tangible and intangible assets of the Loan Parties, except for certain excluded assets, and (b) all of the equity interests of the subsidiaries of the Loan Parties held by the Loan Parties.

We may make voluntary prepayments at any time without payment of a premium or penalty, subject to certain exceptions, and are required to make certain mandatory prepayments of outstanding indebtedness under the Credit Agreement in certain circumstances.

Principal repayments of the Dollar Term Loan, which are due quarterly, began in September 2021 and are equal to 1.0% per annum of the original principal amount of $3.1 billion with any remaining balance payable on the maturity date. The Euro Term Loan does not have any mandatory principal repayments during its term, however in September and December 2021, we made voluntary prepayments totaling €416.7 million or $502.0 million.

The Credit Agreement contains customary representations and warranties and customary affirmative and negative covenants applicable to the Company and its restricted subsidiaries, including, among other things, restrictions on indebtedness, liens, investments, mergers, dispositions, prepayment of junior indebtedness and dividends and other distributions. The Credit Agreement contains financial covenants that require the Company and its restricted subsidiaries to (a) not exceed a maximum first lien secured net leverage ratio and (b) not fall below a minimum interest coverage ratio, provided that such covenants apply only to the Revolving Credit Facility and are applicable only if amounts are drawn (or non-cash collateralized letters of credit in excess of $50 million are outstanding) under the Revolving Credit Facility. The Credit Agreement also contains customary events of default relating to, among other things, failure to make payments, breach of covenants and breach of representations.

2029 Senior Secured Notes

2029 Notes. On April 29, 2021, Jazz Securities Designated Activity Company, or Jazz Securities, a direct wholly owned subsidiary of the Company, closed the offering of the Secured Notes in a private placement. We used the proceeds from the Secured Notes to fund, in part, the cash consideration payable in connection with the GW Acquisition.

Interest on the Secured Notes is payable semi-annually in arrears on January 15 and July 15 of each year, beginning on January 15, 2022, at a rate of 4.375% per year. The Secured Notes mature on January 15, 2029.

The Secured Notes are jointly and severally guaranteed by the Company and each of its restricted subsidiaries, other than Jazz Securities, that is a borrower, or a guarantor, under the Credit Agreement. The Secured Notes and related guarantees are secured by a first priority lien (subject to permitted liens and certain other exceptions), equally and ratably with the Credit Agreement, on the collateral securing the Credit Agreement.

Except as described below, the Secured Notes may not be optionally redeemed before July 15, 2024. Thereafter, some or all of the Secured Notes, may be redeemed at any time and from time to time at a specified redemption prices, plus accrued and unpaid interest, if any, to, but excluding, to the redemption date. Jazz Securities may redeem all but not part of the Secured Notes at its option at any time in connection with certain tax-related events and may redeem some or all of the Secured Notes at any time and from time to time prior to July 15, 2024 at a price equal to 100% of the principal amount of the Secured Notes to be redeemed plus a “make whole” premium, plus accrued and unpaid interest, if any, to, but excluding, the redemption date. In addition, Jazz Securities may redeem up to 40% of the aggregate principal amount of the Secured Notes at any time and from time to time prior to July 15, 2024, with the net proceeds of certain equity offerings at a price of 104.375% of the principal amount of such Secured Notes, plus accrued and unpaid interest, if any, to, but excluding, the redemption date. In addition, during each of the three consecutive twelve-month periods commencing on the issue date of the Secured Notes, Jazz Securities may redeem up to 10% of the original aggregate initial principal amount of the Secured Notes at a redemption price of 103% of the principal amount of such Secured Notes, plus accrued and unpaid interest, if any, to, but excluding, the redemption date.

If Jazz undergoes a change of control, Jazz Securities will be required to make an offer to purchase all of the Secured Notes at a purchase price in cash equal to 101% of the principal amount thereof, plus accrued and unpaid interest, if any, to, but excluding, the date of repurchase, subject to certain exceptions.

The indenture governing the Secured Notes contains customary affirmative covenants and negative covenants applicable to the Company and its restricted subsidiaries, including, among other things, restrictions on indebtedness, liens, investments, mergers, dispositions, prepayment of junior indebtedness and dividends and other distributions. If Jazz Securities or the Company’s restricted subsidiaries engage in certain asset sales, Jazz Securities will be required under certain circumstances to make an offer to purchase the Secured Notes at 100% of the principal amount, plus accrued and unpaid interest, if any, to, but excluding, the repurchase date.

As of December 31, 2021, the interest rate and effective interest rate on the Secured Notes were 4.375% and 4.64%, respectively.

Exchangeable Senior Notes

2026 Notes. In the second quarter of 2020, Jazz Investments I Limited, our wholly owned subsidiary, completed a private placement of $1.0 billion principal amount of the 2026 Notes. We used a portion of the net proceeds from this offering to repurchase for cash $332.9 million aggregate principal amount of the 2021 Notes through privately-negotiated transactions concurrently with the offering of the 2026 Notes. Interest on the 2026 Notes is payable semi-annually in cash in arrears on June 15 and December 15 of each year, beginning on December 15, 2020, at a rate of 2.00% per year. In certain circumstances, we may be required to pay additional amounts as a result of any applicable tax withholding or deductions required in respect of payments on the 2026 Notes. The 2026 Notes mature on June 15, 2026, unless earlier exchanged, repurchased or redeemed.

The holders of the 2026 Notes have the ability to require us to repurchase all or a portion of their 2026 Notes for cash in the event we undergo certain fundamental changes, such as specified change of control transactions, our liquidation or dissolution or the delisting of our ordinary shares from any of The New York Stock Exchange, The Nasdaq Global Market, The Nasdaq Global Select Market or The Nasdaq Capital Market (or any of their respective successors). Additionally, the terms and covenants in the indenture related to the 2026 Notes include certain events of default after which the 2026 Notes may be due and payable immediately. Prior to June 15, 2026, we may redeem the 2026 Notes, in whole but not in part, subject to compliance with certain conditions, if we have, or on the next interest payment date would, become obligated to pay to the holder of any 2026 Notes additional amounts as a result of certain tax-related events. We also may redeem the 2026 Notes on or after June 20, 2023 and prior to March 15, 2026, in whole or in part, if the last reported sale price per ordinary share has been at least 130% of the exchange price then in effect for at least 20 trading days (whether or not consecutive) during any 30 consecutive trading day period ending on, and including, the trading day immediately preceding the date on which we provide the notice of redemption.

The 2026 Notes are exchangeable at an initial exchange rate of 6.4182 ordinary shares per $1,000 principal amount of 2026 Notes, which is equivalent to an initial exchange price of approximately $155.81 per ordinary share. Upon exchange, the 2026 Notes may be settled in cash, ordinary shares or a combination of cash and ordinary shares, at our election. Our intent and policy is to settle the principal amount of the 2026 Notes in cash upon exchange. The exchange rate will be subject to adjustment in some events but will not be adjusted for any accrued and unpaid interest. In addition, following certain make-whole fundamental changes occurring prior to the maturity date of the 2026 Notes or upon our issuance of a notice of redemption, we will in certain circumstances increase the exchange rate for holders of the 2026 Notes who elect to exchange their 2026 Notes in connection with that make-whole fundamental change or during the related redemption period. Prior to March 15, 2026, the 2026 Notes will be exchangeable only upon satisfaction of certain conditions and during certain periods, and thereafter, at any time until the close of business on the second scheduled trading day immediately preceding the maturity date.

2024 Notes. In the third quarter of 2017, our wholly owned subsidiary Jazz Investments I Limited, completed a private placement of $575.0 million principal amount of 2024 Notes. We used the net proceeds from this offering to repay $500.0 million in outstanding loans under the revolving credit facility under the amended credit agreement and to pay related fees and expenses. We used the remainder of the net proceeds for general corporate purposes. The 2024 Notes are senior unsecured obligations of Jazz Investments I Limited and are fully and unconditionally guaranteed on a senior unsecured basis by Jazz Pharmaceuticals plc and will rank pari passu in right of payment with the existing 2021 Notes. Interest on the 2024 Notes is payable semi-annually in cash in arrears on February 15 and August 15 of each year, beginning on February 15, 2018, at a rate of 1.50% per year. In certain circumstances, we may be required to pay additional amounts as a result of any applicable tax withholding or deductions required in respect of payments on the 2024 Notes. The 2024 Notes mature on August 15, 2024, unless earlier exchanged, repurchased or redeemed.

The holders of the 2024 Notes have the ability to require us to repurchase all or a portion of their 2024 Notes for cash in the event we undergo certain fundamental changes, such as specified change of control transactions, our liquidation or dissolution or the delisting of our ordinary shares from The Nasdaq Global Select Market. Prior to August 15, 2024, we may redeem the 2024 Notes, in whole but not in part, subject to compliance with certain conditions, if we have, or on the next interest payment date would, become obligated to pay to the holder of any 2024 Notes additional amounts as a result of certain tax-related events. We also may redeem the 2024 Notes on or after August 20, 2021, in whole or in part, if the last reported sale price per ordinary share has been at least 130% of the exchange price then in effect for at least 20 trading days (whether or not consecutive) during any 30 consecutive trading day period ending on, and including, the trading day immediately preceding the date on which we provide the notice of redemption.

The 2024 Notes are exchangeable at an initial exchange rate of 4.5659 ordinary shares per $1,000 principal amount of 2024 Notes, which is equivalent to an initial exchange price of approximately $219.02 per ordinary share. Upon exchange, the 2024 Notes may be settled in cash, ordinary shares or a combination of cash and ordinary shares, at our election. Our intent and policy is to settle the principal amount of the 2024 Notes in cash upon exchange. The exchange rate will be subject to adjustment in some events but will not be adjusted for any accrued and unpaid interest. In addition, following certain make-whole fundamental changes occurring prior to the maturity date of the 2024 Notes or upon our issuance of a notice of redemption, we will in certain circumstances increase the exchange rate for holders of the 2024 Notes who elect to exchange their 2024 Notes in connection with that make-whole fundamental change or during the related redemption period. Prior to May 15, 2024, the 2024 Notes will be exchangeable only upon satisfaction of certain conditions and during certain periods, and thereafter, at any time until the close of business on the second scheduled trading day immediately preceding the maturity date.

2021 Notes. In 2014, we completed a private placement of the 2021 Notes with a maturity date of August 15, 2021. Interest on the 2021 Notes was payable semi-annually in cash in arrears on February 15 and August 15 of each year, beginning on February 15, 2015, at a rate of 1.875% per year. The exchange rate was 5.0057 ordinary shares per $1,000 principal amount of 2021 Notes, which was equivalent to an exchange price of approximately $199.77 per ordinary share.

In 2020 we repurchased $356.2 million aggregate principal amount of the 2021 Notes and we repurchased the remaining $218.8 million on maturity in August 2021.

Contractual Obligations

Our primary contractual obligations relate to our outstanding indebtedness, as described above. We also have obligations under lease agreements and third-party manufacturing agreements. For information relating to our scheduled maturities with respect to our long-term debt and our lease liabilities see Note 12 Debt and Note 13 Leases, respectively, and for information relating to our noncancelable purchase commitments due within one year see Note 14 Commitments and Contingencies, included in the Notes to Consolidated Financial Statements, included in Part IV of this Annual Report on Form 10-K.

We also have potential future milestone payments or royalty obligations to third parties under asset purchase, product development, license and other agreements as the timing and likelihood of such milestone payments are not known, and, in the case of royalty obligations, as the amount of such obligations are not estimable. Our contingent obligations to third parties, in the form of development, regulatory and sales-based milestone payments, as of December 31, 2021 included $1,025.0 million across five targets under our strategic collaboration agreement with Codiak, $706.0 million under our amended license agreement with PharmaMar, $610.0 million under asset purchase and collaboration agreements with Redx, $375.0 million under the asset purchase and exclusive license agreement with SpringWorks, $260.0 million in connection with our acquisition of Cavion, $165.0 million to Aerial BioPharma LLC and SK Biopharmaceuticals Co. Ltd in connection with our acquisition of the rights to Sunosi, $155.5 million under our license agreement with Ligand and $391.2 million related to other agreements.

Critical Accounting Policies and Significant Estimates

A critical accounting policy is one that is both important to the portrayal of our financial condition and results of operations and requires management's most difficult, subjective or complex judgments, often as a result of the need to make estimates about the effect of matters that are inherently uncertain. While our significant accounting policies are described in more detail in Note 2, Summary of Significant Accounting Policies, of the Notes to Consolidated Financial Statements included in Part IV of this Annual Report on Form 10-K, we believe the following accounting estimates and policies to be critical.

Revenue Recognition

Revenues are recognized when control of the promised goods or services is transferred to our customers, in an amount that reflects the consideration we expect to be entitled to in exchange for those goods or services.

Product Sales, Net

Product sales revenue is recognized when control has transferred to the customer, which occurs at a point in time, which is typically on delivery to the customer or, in the case of products that are subject to consignment agreements, when the customer removes product from our consigned inventory location for shipment directly to a patient.

A significant portion of our net product revenues is derived from sales of Xywav and Xyrem. We sell Xywav and Xyrem in the U.S. to a single central pharmacy, Express Scripts Specialty Distribution Services, Inc., or ESSDS. In 2021, sales of Xywav and Xyrem to Express Scripts accounted for 58% of our net product sales. We recognize revenues from sales of Xywav and Xyrem within the U.S. when control has transferred to the customer, which occurs when ESSDS removes product from our consigned inventory location at its facility for shipment directly to a patient. We do not accept returns of Xywav or Xyrem from ESSDS.

Items Deducted from Gross Product Sales. Revenues from sales of products are recorded net of government rebates and rebates under managed care plans and commercial payor contracts, estimated allowances for sales returns, government chargebacks, prompt payment discounts, patient coupon programs, and specialty distributor and wholesaler fees. Calculating certain of these items involves estimates and judgments based on sales or invoice data, contractual terms, historical utilization rates, new information regarding changes in applicable regulations and guidelines that would impact the amount of the actual rebates, our expectations regarding future utilization rates and channel inventory data. We review the adequacy of our provisions for sales deductions on a quarterly basis. Amounts accrued for sales deductions are adjusted when trends or significant events indicate that adjustment is appropriate and to reflect actual experience. Because we derive a significant portion of our revenues from sales of Xywav and Xyrem in the U.S. to one specialty pharmacy customer, ESSDS, we have a much higher level of knowledge about each prescription than if we sold the product through the normal pharmaceutical wholesaler channel as we do with most of our other products. The most significant items deducted from gross product sales where we exercise judgment are rebates, sales returns and chargebacks.

The following table presents the activity and ending balances for our sales-related accruals and allowances (in thousands):

	Rebates Payable	Sales Returns Reserve	Chargebacks	Discounts and Distributor Fees	Total
Balance at December 31, 2018	$ 81,114	$ 2,510	$ 408	$ 5,457	$ 89,489
Provision, net	153,930	5,519	41,864	56,041	257,354
Payments/credits	(152,191)	(4,567)	(41,139)	(47,378)	(245,275)
Balance at December 31, 2019	82,853	3,462	1,133	14,120	101,568
Provision, net	288,052	18,448	45,550	69,332	421,382
Payments/credits	(260,020)	(3,542)	(41,390)	(66,659)	(371,611)
Balance at December 31, 2020	110,885	18,368	5,293	16,793	151,339
GW Acquisition	53,872	5	1,322	3,260	58,459
Provision, net	440,776	(1,765)	91,425	125,859	656,295
Payments/credits	(409,818)	(794)	(86,651)	(124,104)	(621,367)
Balance at December 31, 2021	$ 195,715	$ 15,814	$ 11,389	$ 21,808	$ 244,726

Total items deducted from gross product sales were $656.3 million, $421.4 million and $257.4 million, or 17.6%, 15.2% and 10.8% as a percentage of gross product sales, in 2021, 2020 and 2019, respectively. Included in these amounts are immaterial adjustments related to prior-year sales due to changes in estimates. Such amounts represented less than 1% of net product sales for each of the years ended December 31, 2021, 2020 and 2019.

Rebates

We are subject to rebates on sales made under governmental and managed-care pricing programs and commercial payor contracts in the U.S. The largest of these rebates is associated with sales covered by Medicaid. We participate in state government-managed Medicaid programs as well as certain other qualifying federal and state government programs under the terms of which discounts and rebates are provided to participating government entities. We offer rebates and discounts to managed health care organizations and commercial payors in the U.S. In estimating our provisions for rebates, we consider relevant statutes with respect to governmental pricing programs and contractual sales terms with managed-care providers, commercial payors and group purchasing organizations. We estimate the rebate provision based on historical utilization rates, historical payment experience, new information regarding changes in regulations and guidelines that would impact the amount of the actual rebates, our expectations regarding future utilization rates and channel inventory data obtained from our major distributors in accordance with our inventory management agreements. Estimating these rebates is complex, in part due to the time delay between the date of sale and the actual settlement of the liability. We believe that the methodology we use to estimate rebates on product sales made under governmental and managed-care pricing programs is reasonable and appropriate given current facts and circumstances. However, estimates may vary from actual experience.

Rebates were $440.8 million, $288.1 million and $153.9 million, or 11.8%, 10.4% and 6.5% as a percentage of gross product sales, in 2021, 2020 and 2019, respectively. Rebates as a percentage of gross product sales increased in 2021 compared to 2020 primarily due to the entry into additional contracts with commercial payors and the addition of Epidiolex to our product portfolio. Rebates as a percentage of gross product sales increased in 2020 compared to 2019 primarily due to the entry into additional contracts with commercial payors. Rebates as a percentage of gross product sales are expected to increase in 2022 compared to 2021, primarily due to rebate rate increases and additional commercial rebates.

Sales returns

For certain products, we allow customers to return product within a specified period before and after the applicable expiration date and issue credits which may be applied against existing or future invoices. We account for sales returns as a reduction in net revenue at the time a sale is recognized by establishing an accrual in an amount equal to the estimated value of products expected to be returned. The sales return accrual is estimated principally based on historical experience, the level and estimated shelf life of inventory in the distribution channel, our return policy and expected market events including generic competition.

Sales returns were $(1.8) million, $18.4 million and $5.5 million, or (0.05)%, 0.7% and 0.2% as a percentage of gross product sales in 2021, 2020 and 2019, respectively. Sales returns as a percentage of gross product sales decreased in 2021 compared to 2020 driven by a reduction in the returns provision due to lower than estimated actual returns. The increase in sales returns in 2020 compared to 2019 was due to the commencement of a product return policy for certain products in 2020. Sales returns as a percentage of gross product sales did not change materially in 2020 compared to 2019. Sales returns as a percentage of gross product sales are not expected to change materially in 2022 compared to 2021.

Chargebacks

We participate in chargeback programs with a number of entities, principally Federal Supply Schedule, Group Purchasing Organizations, and other public parties, under which pricing on products below wholesalers' list prices is provided to participating entities. These entities purchase product through wholesalers at the contract price and the wholesalers charge back to us the difference between their acquisition cost and the lower negotiated price. We record the difference as allowances against accounts receivable. We determine our estimate of the chargebacks provision primarily based on historical experience on a product and program basis, current contract prices under the chargeback programs and channel inventory data.

Chargebacks were $91.4 million, $45.6 million and $41.9 million, or 2.4%, 1.6% and 1.8% as a percentage of gross product sales in 2021, 2020 and 2019, respectively. Chargebacks as a percentage of gross product sales increased in 2021 compared to 2020 primarily due to the addition of Epidiolex to Jazz's portfolio. Chargebacks as a percentage of gross product sales did not change materially in 2020 compared to 2019. We expect that chargebacks will continue to significantly impact our reported net product sales. Chargebacks as a percentage of gross product sales are not expected to change materially in 2022 compared to 2021.

Discounts and distributor fees

Discounts and distributor fees comprise prompt payment discounts, patient coupon programs and specialty distributor and wholesaler fees. We offer customers a cash discount on gross product sales as an incentive for prompt payment. We estimate provisions for prompt pay discounts based on contractual sales terms with customers and historical payment experience. To help patients afford our products, we have various programs to assist them, including patient assistance programs, a free product voucher program and co-pay coupon programs for certain products. We estimate provisions for these programs primarily based on expected program utilization, adjusted as necessary to reflect our actual experience on a product and program basis. Specialty distributor and wholesaler fees comprise fees for distribution of our products. We estimate provisions for distributor and wholesaler fees primarily based on sales volumes and contractual terms with our distributors.

Discounts and distributor fees were $125.9 million, $69.3 million and $56.0 million, or 3.4%, 2.5% and 2.4% as a percentage of gross product sales in 2021, 2020 and 2019, respectively. Discounts and distributor fees as a percentage of gross product sales increased in 2021 compared to 2020 primarily due to the addition of Epidiolex to Jazz's portfolio. Discounts and distributor fees as a percentage of gross product sales did not change materially in 2020 compared to 2019. We expect that discounts and distributor fees as a whole will continue to significantly impact our reported net product sales. Discounts and distributor fees as a percentage of gross product sales are not expected to change materially in 2022 compared to 2021.

Acquisitions and Valuation of Intangibles

We make certain judgments to determine whether transactions should be accounted for as acquisitions of assets or as business combinations. If it is determined that substantially all of the fair value of gross assets acquired in a transaction is concentrated in a single asset (or a group of similar assets), the transaction is treated as an acquisition of assets. We evaluate the inputs, processes, and outputs associated with the acquired set of activities. If the assets in a transaction include an input and a substantive process that together significantly contribute to the ability to create outputs, the transaction is treated as an acquisition of a business.

We account for business combinations using the acquisition method of accounting, which requires that assets acquired and liabilities assumed generally be recorded at their fair values as of the acquisition date. Goodwill represents the excess of the acquisition consideration over the fair value of assets acquired and liabilities assumed. We test goodwill for impairment annually in October and when events or changes in circumstances indicate that the carrying value may not be recoverable. We have determined that we operate in a single segment and have a single reporting unit associated with the development and commercialization of pharmaceutical products. In performing the annual impairment test, the fair value of the reporting unit is compared to its corresponding carrying value, including goodwill. If the carrying value exceeds the fair value of the reporting unit an impairment loss will be recognized for the amount by which the reporting unit's carrying amount exceeds its fair value, not to exceed the carrying amount of goodwill. We have determined the fair value of our single reporting unit to be equal to our market capitalization, as determined by our traded share price, plus a control premium. The control premium used was based on a review of such premiums identified in recent acquisitions of companies of similar size and in similar industries. We performed our annual goodwill impairment test in October 2021 and concluded that goodwill was not impaired as the fair value of the reporting unit significantly exceeded its carrying amount, including goodwill. As of December 31, 2021, we had $1.8 billion of goodwill resulting from acquisitions accounted for as business combinations.

In transactions accounted for as acquisitions of assets, no goodwill is recorded and contingent consideration such as payments upon achievement of various developmental, regulatory and commercial milestones generally is not recognized at the acquisition date. In an asset acquisition, upfront payments allocated to IPR&D projects at the acquisition date are expensed unless there is an alternative future use. In addition, product development milestones are expensed upon achievement.

Valuation of Intangible Assets

We have acquired, and expect to continue to acquire, intangible assets through asset acquisitions or business combinations. When significant identifiable intangible assets are acquired, we engage an independent third party valuation firm to assist in determining the fair values of these assets as of the acquisition date. Discounted cash flow models are typically used in these valuations, which require the use of significant estimates and assumptions, including but not limited to:

- estimating the timing of and expected costs to complete the in-process projects;
- projecting regulatory approvals;
- estimating future cash flows including revenues and operating profits resulting from completed products and in-process projects; and
- developing appropriate discount rates and probability rates by project.

We believe the fair values that we assign to the intangible assets acquired are based upon reasonable estimates and assumptions given available facts and circumstances as of the acquisition dates. No assurance can be given, however, that the underlying assumptions used to estimate expected cash flows will transpire as estimated. In addition, we are required to estimate the period of time over which to amortize the intangible assets, which requires significant judgment.

Impairment of Intangible Assets

Finite-lived intangible assets consist primarily of purchased developed technology and are amortized on a straight-line basis over their estimated useful lives, which range from two to 20 years. The estimated useful lives associated with intangible assets are consistent with the estimated lives of the products and may be modified when circumstances warrant. Intangible assets with finite lives are reviewed for impairment whenever events or circumstances indicate that the carrying value of an asset may not be recoverable. Events giving rise to impairment are an inherent risk in the pharmaceutical industry and cannot be predicted. Factors that we consider in deciding when to perform an impairment review include significant under-performance of a product in relation to expectations, significant negative industry or economic trends, and significant changes or planned changes in our use of the assets. An impairment loss would be recognized when estimated undiscounted future cash flows expected to result from the use of the asset and its eventual disposition are less than its carrying amount. Estimating future cash flows related to an intangible asset involves estimates and assumptions. If our assumptions are not correct, there could be an impairment loss or, in the case of a change in the estimated useful life of the asset, a change in amortization expense.

IPR&D is not amortized but is tested for impairment annually or when events or circumstances indicate that the fair value may be below the carrying value of the asset. If the carrying value of the assets is not expected to be recovered, the assets are written down to their estimated fair values.

As of December 31, 2021, we had $7.0 billion of finite-lived intangible assets, which included $4.9 billion associated with the Epidiolex intangible asset which we acquired in the GW Acquisition.

We did not recognize an impairment charge related to our intangible assets in 2021 or 2019. In 2020, we recorded an acquired in-process research and development, or IPR&D, asset impairment charge of $136.1 million following the decision to stop enrollment in our Phase 3 clinical study of defibrotide for the prevention of VOD due to a determination that the study is highly unlikely to reach one of its primary endpoints.

Please refer to Note 10, Goodwill and Intangible Assets, of the Notes to Consolidated Financial Statements included in Part IV of this Annual Report on Form 10-K, for further information about our intangible assets and the remaining useful lives of our finite-lived intangible assets as of December 31, 2021.

Income Taxes

We use the asset and liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are determined based on differences between the financial statement carrying amount and the tax basis of assets and liabilities and are measured using enacted tax rates and laws that will be in effect when the differences are expected to reverse. We provide a valuation allowance when it is more-likely-than-not that deferred tax assets will not be realized.

Our most significant tax jurisdictions are Ireland, the U.K. and the U.S. Significant estimates are required in determining our expense for income taxes. Some of these estimates are based on management’s interpretations of jurisdiction-specific tax laws or regulations and the likelihood of settlement related to tax audit issues. Various internal and external factors may have favorable or unfavorable effects on our future effective income tax rate. These factors include, but are not limited to, changes in tax laws, regulations and/or rates, changing interpretations of existing tax laws or regulations, changes in estimates of prior years’ items, the impact of accounting for share-based compensation, changes in our international organization, likelihood of settlement, and changes in overall levels of income before taxes.

Realization of our deferred tax assets is dependent upon the generation of future taxable income, the amount and timing of which are uncertain. In evaluating our ability to recover our deferred tax assets, we consider all available positive and negative evidence, including cumulative income in recent fiscal years, our forecast of future taxable income exclusive of certain reversing temporary differences and significant risks and uncertainties related to our business. In determining future taxable income, we are responsible for assumptions utilized including the amount of state, federal and international pre-tax operating income, the reversal of certain temporary differences and the implementation of feasible and prudent tax planning strategies. These assumptions require significant judgment about the forecasts of future taxable income in applicable tax jurisdictions, which are based on our commercial experience to date and are consistent with the plans and estimates that we are using to manage our underlying business.

We maintain a valuation allowance against certain other deferred tax assets where realizability is not certain. We periodically evaluate the likelihood of the realization of deferred tax assets and reduce the carrying amount of these deferred tax assets by a valuation allowance to the extent we believe a portion will not be realized. This determination depends on a variety of factors, some of which are subjective, including our recent cumulative earnings experience by taxing jurisdiction, expectations of future taxable income, carryforward periods available to us for tax reporting purposes, various income tax strategies and other relevant factors. If we determine that the deferred tax assets are not realizable in a future period, we would record material changes to income tax expense in that period.

We have also provided for unrecognized tax benefits that we believe are not more-likely-than-not to be sustained upon examination by tax authorities. The evaluation of unrecognized tax benefits is based on factors that include, but are not limited to, changes in tax law, the measurement of tax positions taken or expected to be taken in tax returns, the effective settlement of matters subject to audit, new audit activity and changes in facts or circumstances related to a tax position. We evaluate unrecognized tax benefits on a quarterly basis and adjust the level of the liability to reflect any subsequent changes in the relevant facts surrounding the uncertain positions. Our liabilities for unrecognized tax benefits can be relieved only if the contingency becomes legally extinguished through either payment to the taxing authority or the expiration of the statute of limitations, the recognition of the benefits associated with the position meet the more-likely-than-not threshold or the liability becomes effectively settled through the examination process. We consider matters to be effectively settled once the taxing authority has completed all of its required or expected examination procedures, including all appeals and administrative reviews. We also accrue for potential interest and penalties related to unrecognized tax benefits in income tax expense (benefit).

Recent Accounting Pronouncements

For a discussion of recent accounting pronouncements, please see Note 2, Summary of Significant Accounting Policies, of the Notes to Consolidated Financial Statements included in Part IV of this Annual Report on Form 10-K.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

Interest Rate Risk. The primary objectives of our investment policy, in order of priority, are as follows: safety and preservation of principal and diversification of risk; liquidity of investments sufficient to meet cash flow requirements; and competitive yield. Although our investments are subject to market risk, our investment policy specifies credit quality standards for our investments and limits the amount of credit exposure from any single issue, issuer or certain types of investment. Our investment policy allows us to maintain a portfolio of cash equivalents and short-term investments in a variety of securities, including U.S. federal government and federal agency securities, corporate bonds or commercial paper issued by U.S. corporations, money market instruments, certain qualifying money market mutual funds, certain repurchase agreements, and tax-exempt obligations of states, agencies and municipalities in the U.S. Our cash equivalents as of December 31, 2021 consist of money market funds which are not subject to significant interest rate risk.

We are exposed to risks associated with changes in interest rates in connection with our term loan borrowings. In May 2021 we entered into a credit agreement, or the Credit Agreement, that provides for (i) a seven-year $3.1 billion term loan B facility, or the Dollar Term Loan, (ii) a seven-year €625.0 million term loan B facility, or the Euro Term Loan and, together with the Dollar Term Loan, collectively known as the Term Loan and (iii) a five-year $500.0 million revolving credit facility, or the Revolving Credit Facility. We used the proceeds from the Term Loan (i) to repay in full $575.9 million under that certain credit agreement, dated as of June 18, 2015 (as amended) among the Company, and certain of our other subsidiaries as borrowers, the lenders party thereto and Bank of America, N.A., as administrative agent and collateral agent, or the Existing Credit Agreement, (ii) to fund, in part, the cash consideration payable in connection with the GW Acquisition and (iii) to pay related fees and expenses. There were no borrowings outstanding under the Revolving Credit Facility as of December 31, 2021. In September and December 2021, we made voluntary prepayments totaling €416.7 million or $502.0 million on the Euro Term Loan. The Dollar Term Loan is subject to a London Inter-Bank Offering Rate, or LIBOR, floor of 0.50%. Based on the outstanding borrowings of $3.3 billion as of December 31, 2021, a hypothetical 1% increase or

decrease in interest rates, above the LIBOR floor in the case of Dollar Term Loan borrowings, would increase or decrease net income for 2022 by approximately $33.2 million.

In April 2021, we issued $1.5 billion in aggregate principal amount of 4.375% senior secured notes, due 2029, or the Secured Notes. In 2017, we completed a private placement of $575.0 million aggregate principal amount of 1.50% exchangeable senior notes due 2024, or the 2024 Notes, and in June 2020, we completed a private offering of $1.0 billion aggregate principal amount of 2.00% exchangeable senior notes due 2026, or the 2026 Notes.

The Secured Notes, the 2024 Notes and the 2026 Notes have fixed annual interest rates of 4.375%, 1.50% and 2.00%, respectively, and we therefore, do not have economic interest rate exposure on the Secured Notes, the 2024 Notes and the 2026 Notes. However, the fair values of the Secured Notes, the 2024 Notes and the 2026 Notes are exposed to interest rate risk. Generally, the fair values of the Secured Notes, the 2024 Notes and the 2026 Notes will increase as interest rates fall and decrease as interest rates rise. The fair values of the 2024 Notes and the 2026 Notes are also affected by volatility in our ordinary share price. As of December 31, 2021 the fair values of the Secured Notes, the 2024 Notes and the 2026 Notes were estimated to be approximately $1.6 billion, $576.0 million and $1.1 billion, respectively.

In July 2017, the Financial Conduct Authority, or FCA, the authority that regulates LIBOR, announced it intended to stop compelling banks to submit rates for the calculation of LIBOR after 2021. In a further update, on November 30, 2020, ICE Benchmark Administration, the administrator of LIBOR, with the support of the U.S. Federal Reserve and FCA, announced plans to consult on ceasing publication of LIBOR on December 31, 2021 for only the one week and two month LIBOR tenors, and on June 30, 2023 for all other LIBOR tenors. While this announcement extends the transition period to June 2023, the U.S. Federal Reserve concurrently issued a statement advising banks to stop new LIBOR issuances by the end of 2021. The Alternative Reference Rates Committee, or ARRC, in the U.S. has proposed that the Secured Overnight Financing Rate, or SOFR, is the rate that represents best practice as the alternative to the U.S. dollar, or USD, LIBOR for use in derivatives and other financial contracts that are currently indexed to USD LIBOR. ARRC has proposed a paced market transition plan to SOFR from USD LIBOR and organizations are currently working on industry wide and company specific transition plans as it relates to derivatives and cash markets exposed to USD LIBOR. We currently have a USD LIBOR cross currency swap which matures in March 2022; as such, the impact of Inter-Bank Offering Rate, or IBOR, reform is not expected to be material.

Foreign Exchange Risk. We have significant operations in Europe as well as in the U.S. The functional currency of each foreign subsidiary is generally the local currency. We are exposed to foreign currency exchange risk as the functional currency financial statements of foreign subsidiaries are translated to U.S. dollars. The assets and liabilities of our foreign subsidiaries having a functional currency other than the U.S. dollar are translated into U.S. dollars at the exchange rate prevailing at the balance sheet date, and at the average exchange rate for the reporting period for revenue and expense accounts. The cumulative foreign currency translation adjustment is recorded as a component of accumulated other comprehensive loss in shareholders' equity. The reported results of our foreign subsidiaries will be influenced by their translation into U.S. dollars by currency movements against the U.S. dollar. Our primary currency translation exposure is related to our subsidiaries that have functional currencies denominated in sterling and euro. A hypothetical 10% strengthening or weakening in the rates used to translate the results of our foreign subsidiaries that have functional currencies denominated in sterling and euro would have increased or decreased net income for the year ended December 31, 2021 by approximately $14.6 million and $9.9 million, respectively.

Transactional exposure arises where transactions occur in currencies other than the functional currency. Transactions in foreign currencies are recorded at the exchange rate prevailing at the date of the transaction. The resulting monetary assets and liabilities are translated into the appropriate functional currency at exchange rates prevailing at the balance sheet date and the resulting gains and losses are reported in foreign exchange gain (loss) in the consolidated statements of income (loss). As of December 31, 2021, our exposure to transaction risk primarily related to the translation of our Euro Term Loan and sterling and euro denominated net monetary liabilities, including intercompany loans, held by subsidiaries with a U.S. dollar functional currency.

In order to hedge our exposure to foreign currency exchange risk associated with our Euro Term Loan, we entered into a cross-currency interest rate swap contract in May 2021 with a maturity date of March 31, 2022. The terms of this contract convert the principal repayments and interest payments on our Euro Term Loan into U.S. dollar. As of December 31, 2021, the cross-currency interest rate swap had a notional amount of $251.0 million which is designated for accounting purposes as a fair value hedge. The net liability fair value of the cross currency swap was $15.2 million as of December 31, 2021. The carrying amount of the Euro Term Loan and the fair value of the cross-currency interest rate swap contract will be remeasured with changes in the euro to U.S. dollar foreign exchange rates recognized within foreign exchange gain (loss) in the consolidated statements of income (loss). The impact of a hypothetical increase or decrease in the euro to U.S. dollar exchange rate on the fair value of our cross-currency interest rate swap contract would be offset by a change in the value of the Euro Term Loan.

We have entered into foreign exchange forward contracts to manage the currency risk associated with the translation of our other sterling and euro-denominated net monetary liabilities, including intercompany loans. These foreign exchange

forward contracts are not designated as hedges; gains and losses on these derivative instruments are designed to offset gains and losses on the underlying balance sheet exposures. As of December 31, 2021, we held foreign exchange forward contracts with notional amounts totaling $347.2 million. The net liability fair value of outstanding foreign exchange forward contracts was $2.6 million as of December 31, 2021. Based on our foreign currency exchange rate exposures as of December 31, 2021, a hypothetical 10% adverse fluctuation in exchange rates would decrease the fair value of our foreign exchange forward contracts by approximately $15.4 million as of December 31, 2021. The resulting loss on these forward contracts would be offset by a positive impact on the underlying monetary assets and liabilities.

Item 8. Financial Statements and Supplementary Data

Our consolidated financial statements as listed below are included in this Annual Report on Form 10-K as pages F-1 through F-44.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

Not applicable.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures. We have carried out an evaluation under the supervision and with the participation of management, including our principal executive officer and principal financial officer, of our disclosure controls and procedures (as defined in Rule 13a-15(e) of the Exchange Act) as of the end of the period covered by this Annual Report on Form 10-K. Based on their evaluation, our principal executive officer and principal financial officer concluded that our disclosure controls and procedures were effective as of December 31, 2021.

Limitations on the Effectiveness of Controls. A control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Because of inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues, if any, within an organization have been detected. Accordingly, our disclosure controls and procedures are designed to provide reasonable, not absolute, assurance that the objectives of our disclosure control system are met and, as set forth above, our principal executive officer and principal financial officer have concluded, based on their evaluation as of the end of the period covered by this report, that our disclosure controls and procedures were effective to provide reasonable assurance that the objectives of our disclosure control system were met.

Changes in Internal Control over Financial Reporting. As discussed above, the GW Acquisition closed on May 5, 2021. The GW Acquisition was accounted for using the acquisition method of accounting. The results of operations of the acquired GW business have been included in our results of operations since May 5, 2021, and we have evaluated and integrated GW's historical internal controls with ours throughout the fiscal year.

During the quarter ended December 31, 2021, there were no changes to our internal control over financial reporting that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Management's Report on Internal Control over Financial Reporting. The following report is provided by management in respect of our internal control over financial reporting (as defined in Rule 13a-15(f) of the Exchange Act):

1. Our management is responsible for establishing and maintaining adequate internal control over financial reporting.
2. Our management used the Committee of Sponsoring Organizations of the Treadway Commission Internal Control - Integrated Framework (2013), or the COSO framework, to evaluate the effectiveness of internal control over financial reporting. Management believes that the COSO framework is a suitable framework for its evaluation of

financial reporting because it is free from bias, permits reasonably consistent qualitative and quantitative measurements of our internal control over financial reporting, is sufficiently complete so that those relevant factors that would alter a conclusion about the effectiveness of our internal control over financial reporting are not omitted and is relevant to an evaluation of internal control over financial reporting.

3. Management has assessed the effectiveness of our internal control over financial reporting as of December 31, 2021 and has concluded that such internal control over financial reporting was effective. There were no material weaknesses in internal control over financial reporting identified by management.

4. KPMG, our independent registered public accounting firm, has audited the consolidated financial statements of Jazz Pharmaceuticals plc as of and for the year ended December 31, 2021, included herein, and has issued an audit report on our internal control over financial reporting, which is included below.

Report of Independent Registered Public Accounting Firm

To the Shareholders and Board of Directors
Jazz Pharmaceuticals plc:

Opinion on Internal Control Over Financial Reporting

We have audited Jazz Pharmaceuticals plc and subsidiaries' (the 'Company') internal control over financial reporting as of December 31, 2021, based on criteria established in *Internal Control - Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission. In our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2021, based on criteria established in *Internal Control - Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2021 and 2020, the related consolidated statements of income (loss), comprehensive income (loss), stockholders' equity, and cash flows for each of the years in the three-year period ended December 31, 2021, and the related notes and financial statement schedule at Item 15(a)2 (collectively, 'the consolidated financial statements'), and our report dated March 1, 2022 expressed an unqualified opinion on those consolidated financial statements.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying Managements Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audit also included performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ KPMG

Dublin, Ireland
March 1, 2022

Item 9B. Other Information

Not applicable.

Item 9.C Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable.

PART III

Certain information required by Part III is omitted from this Annual Report on Form 10-K and incorporated by reference to our definitive proxy statement for our 2022 annual general meeting of shareholders, or our 2022 Proxy Statement, to be filed pursuant to Regulation 14A of the Securities Exchange Act of 1934, as amended, or Exchange Act. If our 2022 Proxy Statement is not filed within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K, the omitted information will be included in an amendment to this Annual Report on Form 10-K filed not later than the end of such 120-day period.

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this item is to be included in our 2022 Proxy Statement as follows and is incorporated by reference:

- The information relating to our directors and nominees for director is to be included in the section entitled “Proposal 1—Election of Directors;”
- The information relating to our executive officers is to be included in the section entitled “Executive Officers;”
- The information relating to our audit committee, audit committee financial expert and procedures by which shareholders may recommend nominees to our board of directors is to be included in the section entitled “Corporate Governance and Board Matters;” and
- If required, the information regarding compliance with Section 16(a) of the Exchange Act is to be included in the section entitled “Delinquent Section 16(a) Reports.”

Such information is incorporated herein by reference to our 2022 Proxy Statement, provided that if the 2022 Proxy Statement is not filed within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K, the omitted information will be included in an amendment to this Annual Report on Form 10-K filed not later than the end of such 120-day period.

Our Code of Conduct applies to all of our employees, directors and officers, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions, and those of our subsidiaries. The Code of Conduct is available on our website at *www.jazzpharmaceuticals.com* under the section entitled “About” under “Corporate Ethics.” We intend to satisfy the disclosure requirements under Item 5.05 of the SEC Form 8-K regarding an amendment to, or waiver from, a provision of our Code of Conduct by posting such information on our website at the website address and location specified above.

Item 11. Executive Compensation

The information required by this item is to be included in our 2022 Proxy Statement under the sections entitled “Executive Compensation,” “Director Compensation,” “Corporate Governance and Board Matters—Compensation Committee Interlocks and Insider Participation” and “Corporate Governance and Board Matters—Compensation Committee Report” and is incorporated herein by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this item with respect to equity compensation plans is to be included in our 2022 Proxy Statement under the section entitled “Equity Compensation Plan Information” and the information required by this item with respect to security ownership of certain beneficial owners and management is to be included in our 2022 Proxy Statement under the section entitled “Security Ownership of Certain Beneficial Owners and Management” and in each case is incorporated herein by reference.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this item is to be included in our 2022 Proxy Statement under the sections entitled "Certain Relationships and Related Party Transactions" and "Corporate Governance and Board Matters—Independence of the Board of Directors" and is incorporated herein by reference.

Item 14. Principal Accountant Fees and Services

The information required by this item is to be included in our 2022 Proxy Statement under the section entitled "Proposal 2—On a Non-Binding Advisory Basis, Ratify Appointment of Independent Registered Accounting Firm and, On a Binding Basis, Authorize the Board of Directors, Acting Through the Audit Committee, to Determine the Independent Auditors' Remuneration" and is incorporated herein by reference.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a) The following documents are filed as part of this Annual Report on Form 10-K:

1. Financial Statements:

See Consolidated Financial Statements in Part II, Item 8 of this Annual Report on Form 10-K.

2. Financial Statement Schedules:

The following financial statement schedule of Jazz Pharmaceuticals plc is filed as part of this Annual Report on Form 10-K on page F-51 and should be read in conjunction with the consolidated financial statements of Jazz Pharmaceuticals plc.

Schedule II: Valuation and Qualifying Accounts

All other schedules are omitted because they are not applicable, not required under the instructions, or the requested information is shown in the consolidated financial statements or related notes thereto.

(b) Exhibits—The following exhibits are included herein or incorporated herein by reference:

Exhibit Number	Description of Document
2.1	Agreement and Plan of Merger and Reorganization, dated as of September 19, 2011, by and among Azur Pharma Limited (now Jazz Pharmaceuticals plc), Jaguar Merger Sub Inc., Jazz Pharmaceuticals, Inc. and Seamus Mulligan, solely in his capacity as the Indemnitors' Representative (incorporated herein by reference to Exhibit 2.1 in Jazz Pharmaceuticals, Inc.'s Current Report on Form 8-K (File No. 001-33500) filed with the SEC on September 19, 2011).
2.2	Letter Agreement, dated as of January 17, 2012, by and among Jazz Pharmaceuticals plc, Jaguar Merger Sub Inc., Jazz Pharmaceuticals, Inc. and Seamus Mulligan, solely in his capacity as the Indemnitors' Representative (incorporated herein by reference to Exhibit 2.2 in Jazz Pharmaceuticals plc's Current Report on Form 8-K (File No. 001-33500), as filed with the SEC on January 18, 2012).
2.3	Agreement and Plan of Merger, dated as of April 26, 2012, by and among Jazz Pharmaceuticals plc, Jewel Merger Sub Inc., EUSA Pharma Inc., and Essex Woodlands Health Ventures, Inc., Mayflower L.P., and Bryan Morton, in their capacity as the representatives of the equity holders of EUSA Pharma Inc. (incorporated herein by reference to Exhibit 2.1 in Jazz Pharmaceuticals plc's Current Report on Form 8-K (File No. 001-33500), as filed with the SEC on April 27, 2012).
2.4	Assignment, dated as of June 11, 2012, by and among Jazz Pharmaceuticals plc and Jazz Pharmaceuticals, Inc. (incorporated herein by reference to Exhibit 2.1B in Jazz Pharmaceuticals plc's Current Report on Form 8-K (File No. 001-33500), as filed with the SEC on June 12, 2012).
2.5	Tender Offer Agreement, dated December 19, 2013, by and among Jazz Pharmaceuticals Public Limited Company, Jazz Pharmaceuticals Italy S.r.l. and Gentium S.p.A. (incorporated herein by reference to Exhibit 2.1 in Jazz Pharmaceuticals plc's Current Report on Form 8-K/A (File No. 001-33500), as filed with the SEC on December 20, 2013).
2.6†	Asset Purchase Agreement, dated January 13, 2014, by and among Jazz Pharmaceuticals International III Limited, Aerial BioPharma, LLC and Jazz Pharmaceuticals plc (incorporated herein by reference to Exhibit 2.1 in Jazz Pharmaceuticals plc's Current Report on Form 8-K (File No. 001-33500), as filed with the SEC on January 13, 2014).

2.7†	Assignment Agreement, dated July 1, 2014, by and among Jazz Pharmaceuticals International II Limited, Sigma-Tau Pharmaceuticals, Inc., Jazz Pharmaceuticals plc and Gentium S.p.A. (incorporated herein by reference to Exhibit 2.1 in Jazz Pharmaceuticals plc's Current Report on Form 8-K (File No. 001-33500), as filed with the SEC on August 5, 2014).
2.8	Amended and Restated Agreement for the Acquisition of the Topaz Portfolio Business of Jazz Pharmaceuticals plc, dated March 20, 2015, between Jazz Pharmaceuticals plc and Essex Bidco Limited (incorporated herein by reference to Exhibit 2.1 in Jazz Pharmaceuticals plc's Current Report on Form 8-K (File No. 001-33500), as filed with the SEC on March 23, 2015).
2.9	Agreement and Plan of Merger, dated as of May 27, 2016, by and among Jazz Pharmaceuticals plc, Plex Merger Sub, Inc., and Celator Pharmaceuticals, Inc. (incorporated herein by reference to Exhibit 2.1 in Jazz Pharmaceuticals plc's Current Report on Form 8-K (File No. 001-33500), as filed with the SEC on May 31, 2016).
2.10‡	Transaction Agreement, dated as of February 3, 2021, by and among Jazz Pharmaceuticals UK Holdings Limited, Jazz Pharmaceuticals Public Limited Company and GW Pharmaceuticals PLC (incorporated herein by reference to Exhibit 2.1 in Jazz Pharmaceuticals plc's Current Report on Form 8-K (File No. 001-33500), as filed with the SEC on February 4, 2021).
3.1	Amended and Restated Memorandum and Articles of Association of Jazz Pharmaceuticals plc, as amended on August 4, 2016 (incorporated herein by reference to Exhibit 3.1 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2016, as filed with the SEC on August 9, 2016).
4.1	Reference is made to Exhibit 3.1.
4.2A	Investor Rights Agreement, dated July 7, 2009 by and between Jazz Pharmaceuticals, Inc. and the other parties named therein (incorporated herein by reference to Exhibit 10.88 in Jazz Pharmaceuticals, Inc.'s Current Report on Form 8-K (File No. 001-33500), as filed with the SEC on July 7, 2009).
4.2B	Assignment, Assumption and Amendment Agreement, dated as of January 18, 2012, by and among Jazz Pharmaceuticals, Inc., Jazz Pharmaceuticals plc and the other parties named therein (incorporated herein by reference to Exhibit 4.7B in the Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2011, as filed by Jazz Pharmaceuticals plc on behalf of and as successor to Jazz Pharmaceuticals, Inc. with the SEC on February 28, 2012).
4.3A	Indenture, dated as of August 23, 2017, among Jazz Pharmaceuticals Public Limited Company, Jazz Investments I Limited and U.S. Bank National Association (incorporated herein by reference to Exhibit 4.1 in Jazz Pharmaceuticals plc's Current Report on Form 8-K (File No. 001-33500), as filed with the SEC on August 23, 2017).
4.3B	Form of 1.50% Exchangeable Senior Note due 2024 (incorporated herein by reference to Exhibit 4.1 in Jazz Pharmaceuticals plc's Current Report on Form 8-K (File No. 001-33500), as filed with the SEC on August 23, 2017).
4.4A	Indenture, dated as of June 11, 2020 among Jazz Pharmaceuticals Public Limited Company, Jazz Investments I Limited and U.S. Bank National Association (incorporated herein by reference to Exhibit 4.1 in Jazz Pharmaceuticals plc's Current Report on Form 8-K (File No. 001-033500), as filed with the SEC on June 11, 2020).
4.4B	Form of 2.000% Exchangeable Senior Note due 2026 (incorporated herein by reference to Exhibit 4.2 in Jazz Pharmaceuticals plc's Current Report on Form 8-K (File No. 001-033500), as filed with the SEC on June 11, 2020).
4.5A	Indenture, dated as of April 29, 2021, among Jazz Securities Designated Activity Company, the guarantors party thereto, U.S. Bank National Association, as trustee and acknowledged by U.S. Bank National Association, as collateral trustee. (incorporated herein by reference to Exhibit 4.1 in Jazz Pharmaceuticals plc's Current Report on Form 8-K (File No. 001-033500), as filed with the SEC on April 29, 2021).
4.5B	Form of 4.375% Senior Notes due 2029 (incorporated herein by reference to Exhibit 4.2 in Jazz Pharmaceuticals plc's Current Report on Form 8-K (File No. 001-033500), as filed with the SEC on April 29, 2021).
4.5C	First Supplemental Indenture, dated as of July 21, 2021, among GW Pharmaceuticals Limited, GW Global Services (International) Limited, GW Pharma Limited, GW Research Limited, GW UK Services Limited and Greenwich Biosciences, Inc., Jazz Securities Designated Activity Company, and U.S. Bank National Association, as trustee under the Indenture, dated as of April 29, 2021 (incorporated herein by reference to Exhibit 4.5C in Jazz Pharmaceuticals, plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2021, as filed with the SEC on August 3, 2021).
4.6	Description of Share Capital.

10.1	Settlement Agreement, dated as of April 5, 2017, by and between Jazz Pharmaceuticals, Inc. and Jazz Pharmaceuticals Ireland Limited, and Roxane Laboratories, Inc., West-Ward Pharmaceuticals Corp., Eurohealth (USA), Inc., and Hikma Pharmaceuticals PLC (incorporated herein by reference to Exhibit 10.1 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2017, as filed with the SEC on August 8, 2017).
10.2	Settlement Agreement, dated as of April 4, 2019, by and among United States of America, acting through the United States Department of Justice and on behalf of the Office of Inspector General of the Department of Health and Human Services, Jazz Pharmaceuticals plc, Jazz Pharmaceuticals, Inc., and Jazz Pharmaceuticals Ireland Ltd. (incorporated herein by reference to Exhibit 10.7 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended March 31, 2019, as filed with the SEC on May 7, 2019).
10.3	Corporate Integrity Agreement, dated as of April 3, 2019, by and between Jazz Pharmaceuticals plc and the Office of Inspector General of the United States Department of Health and Human Services (incorporated herein by reference to Exhibit 10.6 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended March 31, 2019, as filed with the SEC on May 7, 2019).
10.4†	Supply Agreement, dated as of April 1, 2010, by and between Jazz Pharmaceuticals, Inc. and Siegfried (USA) Inc. (incorporated herein by reference to Exhibit 10.54 in Jazz Pharmaceuticals, Inc.'s Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended March 31, 2010, as filed with the SEC on May 6, 2010).
10.5†	Royalty Bearing Licence Agreement and Supply Agreement Re Erwinia-Derived Asparaginase, dated July 22, 2005, between Public Health England (formerly Health Protection Agency) and EUSA Pharma SAS (formerly OPi, S.A.), as amended on each of December 22, 2009, March 23, 2012 and August 8, 2012 (incorporated herein by reference to Exhibit 10.11 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q/A (File No. 001-33500) for the period ended June 30, 2012, as filed with the SEC on August 9, 2012).
10.6	Novation Agreement relating to Royalty Bearing Licence Agreement and Supply Agreement re Erwinia-Derived Asparaginase, dated as of May 13, 2015, by and among EUSA Pharma SAS, the Secretary of State for Health acting through Public Health England and Porton Biopharma Limited (incorporated herein by reference to Exhibit 10.3 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2015, as filed with the SEC on August 5, 2015).
10.7	Contract Variation Agreement by and between Porton Biopharma Limited and Jazz Pharmaceuticals France SAS, dated as of December 20, 2018 (incorporated herein by reference to Exhibit 10.5 in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2018, as filed with the SEC on February 26, 2019).
10.8‡	Master Manufacturing Services Agreement, dated as of October 1, 2015, by and between Jazz Pharmaceuticals Ireland Limited and Patheon Pharmaceuticals Inc. (incorporated herein by reference to Exhibit 10.8 in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2020, as filed with the SEC on February 23, 2021).
10.9A†	Clinical and Commercial Manufacturing and Supply Agreement, dated as of December 22, 2010, between Celator Pharmaceuticals, Inc. and Baxter Oncology GmbH (incorporated herein by reference to Exhibit 10.8 in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the year ended December 31, 2017, as filed with the SEC on February 27, 2018).
10.9B†	Amendment No. 1 Clinical and Commercial Manufacturing and Supply Agreement, dated as of January 18, 2018, by and between Jazz Pharmaceuticals Ireland Limited and Baxter Oncology GmbH (incorporated herein by reference to Exhibit 10.3 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended March 31, 2018, as filed with the SEC on May 8, 2018).
10.10‡	Contract Manufacturing Agreement, dated as of January 20, 2020, by and between Jazz Pharmaceuticals Ireland Limited and Siegfried AG (incorporated herein by reference to Exhibit 10.10 in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2019, as filed with the SEC on February 25, 2020).
10.11A‡	Pharmacy Master Services Agreement, dated as of July 1, 2020, by and between Jazz Pharmaceuticals, Inc. and Express Scripts Specialty Distribution Services, Inc. (incorporated herein by reference to Exhibit 10.2 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2020, as filed with the SEC on August 4, 2020).

10.11B	Amendment No. 1, dated as of July 4, 2021 to Pharmacy Master Services Agreement, dated as of July 1, 2020, by and between Jazz Pharmaceuticals, Inc. and Express Scripts Specialty Distribution Services, Inc. (incorporated herein by reference to Exhibit 10.1A in Jazz Pharmaceuticals, plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2021, as filed with the SEC on August 3, 2021).
10.11C	Amendment No. 2, dated as of July 19, 2021 to Pharmacy Master Services Agreement, dated as of July 1, 2020, by and between Jazz Pharmaceuticals, Inc. and Express Scripts Specialty Distribution Services, Inc. (incorporated herein by reference to Exhibit 10.1B in Jazz Pharmaceuticals, plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2021, as filed with the SEC on August 3, 2021).
10.11D	Amendment No. 3, dated as of December 7, 2021 to Pharmacy Master Services Agreement, dated as of July 1, 2020, by and between Jazz Pharmaceuticals, Inc. and Express Scripts Specialty Distribution Services, Inc.
10.12A‡	Amended and Restated License Agreement, dated as of October 14, 2020, between Pharma Mar, S.A. and Jazz Pharmaceuticals Ireland Limited (incorporated herein by reference to Exhibit 10.12 in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2020, as filed with the SEC on February 23, 2021).
10.12B‡	Amendment No. 1, dated as of May 6, 2021, to Amended and Restated License Agreement, dated as of October 14, 2020, between Pharma Mar, S.A. and Jazz Pharmaceuticals Ireland Limited (incorporated herein by reference to Exhibit 10.2 in Jazz Pharmaceuticals, plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2021, as filed with the SEC on August 3, 2021).
10.13A	Credit Agreement, dated as of June 18, 2015, among Jazz Pharmaceuticals plc, Jazz Securities Limited, Jazz Pharmaceuticals, Inc., Jazz Financing I Limited, Jazz Pharmaceuticals Ireland Limited, the lenders party thereto and Bank of America, N.A., as Collateral Agent, Administrative Agent, Swing Line Lender and L/C Issuer (incorporated herein by reference to Exhibit 10.1 in Jazz Pharmaceuticals plc's Current Report on Form 8-K (File No. 001-33500), as filed with the SEC on June 18, 2015).
10.13B	Amendment No. 1, dated as of July 12, 2016, to Credit Agreement, dated as of June 18, 2015, among Jazz Pharmaceuticals plc, Jazz Securities Limited, Jazz Pharmaceuticals, Inc., Jazz Financing I Limited, Jazz Pharmaceuticals Ireland Limited, the lenders party thereto and Bank of America, N.A., as Collateral Agent, Administrative Agent, Swing Line Lender and L/C Issuer (incorporated herein by reference to Exhibit 10.1 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2016, as filed with the SEC on August 9, 2016).
10.13C	Amendment No. 2, dated as of June 7, 2018, to Credit Agreement, dated as of June 18, 2015 (as previously amended by Amendment No. 1, dated as of July 12, 2016), among Jazz Pharmaceuticals plc, Jazz Securities Designated Activity Company, Jazz Pharmaceuticals, Inc., Jazz Financing I Designated Activity Company, Jazz Pharmaceuticals Ireland Limited, the lenders party thereto and Bank of America, N.A., as Collateral Agent, Administrative Agent, Swing Line Lender and L/C Issuer (incorporated herein by reference to Exhibit 10.4 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2018, as filed with the SEC on August 7, 2018).
10.13D	Amendment No. 3, dated as of April 20, 2021, to Credit Agreement, dated as of June 18, 2015 (as previously amended by Amendment No. 1, dated as of July 12, 2016 and Amendment No.2, dated as of June 7, 2018), among Jazz Pharmaceuticals plc, Jazz Securities Designated Activity Company, Jazz Pharmaceuticals, Inc., Jazz Financing I Designated Activity Company, Jazz Pharmaceuticals Ireland Limited, the lenders party thereto and Bank of America, N.A., as Collateral Agent, Administrative Agent, Swing Line Lender and L/C Issuer (incorporated herein by reference to Exhibit 10.1 in Jazz Pharmaceuticals plc's Current Report on Form 8-K (File No. 001-33500), as filed with the SEC on April 20, 2021.
10.14	Credit Agreement, dated as of May 5, 2021, by and among Jazz Pharmaceuticals Public Limited Company, the other borrowers from time to time party thereto, the lenders and issuing banks from time to time party thereto, Bank of America, N.A., as administrative agent, and U.S. Bank National Association, as collateral trustee (incorporated herein by reference to Exhibit 10.1 in Jazz Pharmaceuticals plc's Current Report on Form 8-K (File No. 001-033500), as filed with the SEC on May 5, 2021).
10.15A	Commercial Lease, dated as of June 2, 2004, by and between Jazz Pharmaceuticals, Inc. and The Board of Trustees of the Leland Stanford Junior University (incorporated herein by reference to Exhibit 10.52 in Jazz Pharmaceuticals, Inc.'s registration statement on Form S-1, as amended (File No. 333-141164), as filed with the SEC on March 27, 2007).

10.15B	First Amendment of Lease, dated June 1, 2009, by and between Jazz Pharmaceuticals, Inc. and Wheatley-Fields, LLC, successor in interest to The Board of Trustees of the Leland Stanford Junior University (incorporated herein by reference to Exhibit 10.86 in Jazz Pharmaceuticals, Inc.'s Current Report on Form 8-K (File No. 001-33500), as filed with the SEC on June 4, 2009).
10.15C	Second Amendment of Lease, dated February 28, 2012, by and between Jazz Pharmaceuticals, Inc. and Wheatley-Fields, LLC, successor in interest to The Board of Trustees of the Leland Stanford Junior University (incorporated herein by reference to Exhibit 10.31 in the Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2011, as filed by Jazz Pharmaceuticals plc on behalf of and as successor to Jazz Pharmaceuticals, Inc. with the SEC on February 28, 2012).
10.16	Lease, dated May 8, 2012, by and between John Ronan and Castle Cove Property Developments Limited and Jazz Pharmaceuticals plc (incorporated herein by reference to Exhibit 10.2 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2012, as filed with the SEC on August 7, 2012).
10.17A	Commercial Lease, dated as of January 7, 2015, by and between The Board of Trustees of the Leland Stanford Junior University and Jazz Pharmaceuticals, Inc. (incorporated herein by reference to Exhibit 10.10 in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2014, as filed with the SEC on February 24, 2015).
10.17B	First Amendment, dated as of January 29, 2018, to Commercial Lease, dated as of January 7, 2015, by and between The Board of Trustees of the Leland Stanford Junior University and Jazz Pharmaceuticals, Inc. (incorporated herein by reference to Exhibit 10.5 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2018, as filed with the SEC on August 7, 2018).
10.17C	Second Amendment, dated as of July 26, 2018, to Commercial Lease, dated as of January 7, 2015, by and between The Board of Trustees of the Leland Stanford Junior University and Jazz Pharmaceuticals, Inc., as previously amended by the First Amendment to Lease, dated as of January 29, 2018 (incorporated herein by reference to Exhibit 10.1 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2018, as filed with the SEC on November 6, 2018).
10.18+	Form of Indemnification Agreement between Jazz Pharmaceuticals plc and its officers and directors (incorporated herein by reference to Exhibit 10.1 in Jazz Pharmaceuticals plc's Current Report on Form 8-K (File No. 001-33500), as filed with the SEC on January 18, 2012).
10.19+	Offer Letter from Jazz Pharmaceuticals, Inc. to Daniel N. Swisher, Jr. (incorporated herein by reference to Exhibit 10.21 in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the year ended December 31, 2017, as filed with the SEC on February 27, 2018).
10.20+	Offer Letter from Jazz Pharmaceuticals, Inc. to Robert Iannone dated as of April 11, 2019 (incorporated herein by reference to Exhibit 10.4 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2019, as filed with the SEC on August 6, 2019).
10.21A+	Employment Agreement, dated as of May 16, 2012 by and between Patricia Carr and Jazz Pharmaceuticals plc (incorporated herein by reference to Exhibit 10.1 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2019, as filed with the SEC on November 5, 2019).
10.21B+	Change in Control Severance Terms, dated as of May 15, 2016, by and between Jazz Pharmaceuticals Ireland Ltd. and Patricia Carr (incorporated herein by reference to Exhibit 10.2 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2019, as filed with the SEC on November 5, 2019).
10.21C+	Change in Control Stock Award Acceleration Agreement, dated as of May 15, 2016 by and between Jazz Pharmaceuticals plc and Patricia Carr (incorporated herein by reference to Exhibit 10.3 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2019, as filed with the SEC on November 5, 2019).
10.22+	Offer Letter, dated as of July 5, 2019 by and between Jazz Pharmaceuticals, Inc. and Neena M. Patil (incorporated herein by reference to Exhibit 10.4 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2019, as filed with the SEC on November 5, 2019).
10.23A+	Employment Contract, dated as of February 22, 2013, by and between Jazz Pharmaceuticals Ireland Limited and Finbar Larkin (incorporated herein by reference to Exhibit 10.27 in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2019, as filed with the SEC on February 25, 2020).

10.23B+	Amendment to Employment Contract, dated as of February 26, 2020, by and between Jazz Pharmaceuticals Ireland Limited and Finbar Larkin ((incorporated herein by reference to Exhibit 10.2 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended March 31, 2020, as filed with the SEC on May 5, 2020).
10.24A+	Employment Contract, dated as of December 14, 2019, by and between Jazz Pharmaceuticals UK Limited and Samantha Pearce (incorporated herein by reference to Exhibit 10.28A in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2019, as filed with the SEC on February 25, 2020).
10.24B+	Amendment to Employment Contract, dated as of April 21, 2020, by and between Jazz Pharmaceuticals UK Limited and Samantha Pearce (incorporated herein by reference to Exhibit 10.4 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended March 31, 2020, as filed with the SEC on May 5, 2020).
10.24C+	Equity Award Letter, dated as of December 9, 2019, by and between Jazz Pharmaceuticals UK Limited and Samantha Pearce (incorporated herein by reference to Exhibit 10.28B in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2019, as filed with the SEC on February 25, 2020).
10.25+	Offer Letter, dated as of February 23, 2020, by and between Jazz Pharmaceuticals, Inc. and Renée Galá (incorporated herein by reference to Exhibit 10.1 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended March 31, 2020, as filed with the SEC on May 5, 2020).
10.26+	Offer Letter, dated as of May 2, 2020, by and between Jazz Pharmaceuticals, Inc. and Kim Sablich (incorporated herein by reference to Exhibit 10.1 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2020, as filed with the SEC on August 4, 2020).
10.27A+	Service Agreement, dated as of May 5, 2021, by and between Chris Tovey and Jazz Pharmaceuticals UK Limited (incorporated herein by reference to Exhibit 10.4 in Jazz Pharmaceuticals, plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2021, as filed with the SEC on August 3, 2021).
10.27B+	Participation Agreement, dated as of May 5, 2021, by and between Chris Tovey and Jazz Pharmaceuticals UK Limited (incorporated herein by reference to Exhibit 10.5 in Jazz Pharmaceuticals, plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2021, as filed with the SEC on August 3, 2021).
10.28A+	Jazz Pharmaceuticals plc 2007 Equity Incentive Plan (incorporated herein by reference to Exhibit 99.3 in Jazz Pharmaceuticals plc's registration statement on Form S-8 (File No. 333-179075), as filed with the SEC on January 18, 2012).
10.28B+	Jazz Pharmaceuticals plc 2007 Equity Incentive Plan Sub-Plan Governing Awards to Participants in the Republic of Ireland (incorporated herein by reference to Exhibit 10.3B in the Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2011, as filed by Jazz Pharmaceuticals plc on behalf of and as successor to Jazz Pharmaceuticals Inc. with the SEC on February 28, 2012).
10.28C+	Form of Notice of Grant of Stock Options and Form of Option Agreement (U.S.) under the Jazz Pharmaceuticals plc 2007 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.27C in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2012, as filed with the SEC on February 26, 2013).
10.28D+	Form of Notice of Grant of Stock Options and Form of Option Agreement (Irish) under Jazz Pharmaceuticals plc 2007 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.27D in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2012, as filed with the SEC on February 26, 2013).
10.28E+	Form of Restricted Stock Unit Grant Notice and Form of Restricted Stock Unit Award Agreement (U.S.) under the Jazz Pharmaceuticals plc 2007 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.27E in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2012, as filed with the SEC on February 26, 2013).
10.28F+	Form of Restricted Stock Unit Grant Notice and Form of Restricted Stock Unit Award Agreement (Irish) under the Jazz Pharmaceuticals plc 2007 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.27F in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2012, as filed with the SEC on February 26, 2013).

10.28G+	Jazz Pharmaceuticals plc 2007 Equity Incentive Plan - Form of Non-U.S. Option Grant Notice and Form of Non-U.S. Option Agreement (approved July 31, 2013) (incorporated herein by reference to Exhibit 10.1 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2013, as filed with the SEC on November 5, 2013).
10.28H+	Jazz Pharmaceuticals plc 2007 Equity Incentive Plan - Form of Non-U.S. Restricted Stock Unit Award Grant Notice and Form of Non-U.S. Restricted Stock Unit Award Agreement (approved July 31, 2013) (incorporated herein by reference to Exhibit 10.2 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2013, as filed with the SEC on November 5, 2013).
10.29A+	Jazz Pharmaceuticals plc 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 99.1 in Jazz Pharmaceuticals plc's registration statement on Form S-8 (File No. 333-179075), as filed with the SEC on January 18, 2012).
10.29B+	Jazz Pharmaceuticals plc 2011 Equity Incentive Plan Sub-Plan Governing Awards to Participants in the Republic of Ireland (incorporated herein by reference to Exhibit 10.39B in the Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2011, as filed by Jazz Pharmaceuticals plc on behalf of and as successor to Jazz Pharmaceuticals Inc. with the SEC on February 28, 2012).
10.29C+	Form of Stock Option Grant Notice and Form of Option Agreement (U.S.) under the Jazz Pharmaceuticals plc 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.7 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2012, as filed with the SEC on August 7, 2012).
10.29D+	Form of Stock Option Grant Notice and Form of Option Agreement (Irish) under the Jazz Pharmaceuticals plc 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.8 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2012, as filed with the SEC on August 7, 2012).
10.29E+	Form of Non-U.S. Option Grant Notice and Form of Non-U.S. Option Agreement under the Jazz Pharmaceuticals plc 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.28E in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2012, as filed with the SEC on February 26, 2013).
10.29F+	Form of Restricted Stock Unit Grant Notice and Form of Restricted Stock Unit Award Agreement (U.S.) under the Jazz Pharmaceuticals plc 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.9 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2012, as filed with the SEC on August 7, 2012).
10.29G+	Form of Restricted Stock Unit Grant Notice and Form of Restricted Stock Unit Award Agreement (Irish) under the Jazz Pharmaceuticals plc 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.10 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2012, as filed with the SEC on August 7, 2012).
10.29H+	Form of Non-U.S. Restricted Stock Unit Grant Notice and Form of Non-U.S. Restricted Stock Unit Agreement under the Jazz Pharmaceuticals plc 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.28H in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2012, as filed with the SEC on February 26, 2013).
10.29I+	Jazz Pharmaceuticals plc 2011 Equity Incentive Plan - Form of U.S. Option Grant Notice and Form of U.S. Option Agreement (approved July 31, 2013) (incorporated herein by reference to Exhibit 10.3 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2013, as filed with the SEC on November 5, 2013).
10.29J+	Jazz Pharmaceuticals plc 2011 Equity Incentive Plan - Form of U.S. Restricted Stock Unit Award Grant Notice and Form of U.S. Restricted Stock Unit Award Agreement (approved July 31, 2013) (incorporated herein by reference to Exhibit 10.4 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2013, as filed with the SEC on November 5, 2013).
10.29K+	Jazz Pharmaceuticals plc 2011 Equity Incentive Plan - Form of Non-U.S. Option Grant Notice and Form of Non-U.S. Option Agreement (approved July 31, 2013) (incorporated herein by reference to Exhibit 10.5 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2013, as filed with the SEC on November 5, 2013).
10.29L+	Jazz Pharmaceuticals plc 2011 Equity Incentive Plan - Form of Non-U.S. Restricted Stock Unit Award Grant Notice and Form of Non-U.S. Restricted Stock Unit Award Agreement (approved July 31, 2013) (incorporated herein by reference to Exhibit 10.6 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2013, as filed with the SEC on November 5, 2013).

10.29M+	Jazz Pharmaceuticals plc 2011 Equity Incentive Plan - Form of Non-U.S. Option Grant Notice and Form of Non-U.S. Option Agreement (incorporated herein by reference to Exhibit 10.1 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended March 31, 2016, as filed with the SEC on May 10, 2016).
10.29N+	Jazz Pharmaceuticals plc 2011 Equity Incentive Plan - Form of Non-U.S. Restricted Stock Unit Grant Notice and Form of Non-U.S. Restricted Stock Unit Award Agreement (incorporated herein by reference to Exhibit 10.2 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended March 31, 2016, as filed with the SEC on May 10, 2016).
10.29O+	Amended and Restated 2011 Equity Incentive Plan (approved August 4, 2016) (incorporated herein by reference to Exhibit 10.8 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2016, as filed with the SEC on August 9, 2016).
10.29P+	Amended and Restated 2011 Equity Incentive Plan (approved November 3, 2016) (incorporated herein by reference to Exhibit 10.2 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2016, as filed with the SEC on November 8, 2016).
10.29Q+	Form of U.S. Restricted Stock Unit Award Grant Notice and Form of U.S. Restricted Stock Unit Award Agreement under the Jazz Pharmaceuticals plc Amended and Restated 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.6 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2016, as filed with the SEC on November 8, 2016).
10.29R+	Form of U.S. Option Grant Notice and Form of U.S. Option Agreement under the Jazz Pharmaceuticals plc Amended and Restated 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.7 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2016, as filed with the SEC on November 8, 2016).
10.29S+	Form of Non-U.S. Restricted Stock Unit Award Grant Notice and Form of Non-U.S. Restricted Stock Unit Award Agreement under the Jazz Pharmaceuticals plc Amended and Restated 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.8 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2016, as filed with the SEC on November 8, 2016).
10.29T+	Form of Non-U.S. Option Grant Notice and Non-U.S. Option Agreement under the Jazz Pharmaceuticals plc Amended and Restated 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.2 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2018, as filed with the SEC on August 7, 2018).
10.29U+	Form of Non-U.S. Restricted Stock Unit Award Grant Notice and Non-U.S. Restricted Stock Unit Award Agreement under the Jazz Pharmaceuticals plc Amended and Restated 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.3 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2018, as filed with the SEC on August 7, 2018).
10.29V+	Form of Non-U.S. Option Grant Notice and Non-U.S. Option Agreement under the Jazz Pharmaceuticals plc 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.4 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended March 31, 2019, as filed with the SEC on May 7, 2019).
10.29W+	Form of Non-U.S. Restricted Stock Unit Award Grant Notice and Non-U.S. Restricted Stock Unit Award Agreement under the Jazz Pharmaceuticals plc 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.5 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended March 31, 2019, as filed with the SEC on May 7, 2019).
10.29X+	Form of U.S. Restricted Stock Unit Award Grant Notice and Form of U.S. Restricted Stock Unit Award Agreement under the Jazz Pharmaceuticals plc Amended and Restated 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.8 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2021, as filed with the SEC on August 3, 2021).
10.29Y+	Form of Non-U.S. Restricted Stock Unit Award Grant Notice and Form of Non-U.S. Restricted Stock Unit Award Agreement under the Jazz Pharmaceuticals plc Amended and Restated 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.9 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2021, as filed with the SEC on August 3, 2021).
10.29Z+	Form of Non-U.S. Restricted Stock Unit Award Grant Notice and Form of Non-U.S. Restricted Stock Unit Award Agreement under the Jazz Pharmaceuticals plc Amended and Restated 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.1 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2021, as filed with the SEC on November 9, 2021).

10.29AA+	Form of U.S. Performance Restricted Stock Unit Award Grant Notice and Form of U.S. Performance Restricted Stock Unit Award Agreement under the Jazz Pharmaceuticals plc Amended and Restated 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.6 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2021, as filed with the SEC on August 3, 2021).
10.29BB+	Form of Non-U.S. Performance Restricted Stock Unit Award Grant Notice and Form of Non-U.S. Performance Restricted Stock Unit Award Agreement under the Jazz Pharmaceuticals plc Amended and Restated 2011 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.7 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2021, as filed with the SEC on August 3, 2021).
10.30+	Jazz Pharmaceuticals plc Amended and Restated Directors Deferred Compensation Plan (incorporated herein by reference to Exhibit 99.6 in Jazz Pharmaceuticals plc's registration statement on Form S-8 (File No. 333-179075), as filed with the SEC on January 18, 2012).
10.31A+	Jazz Pharmaceuticals plc Amended and Restated 2007 Non-Employee Directors Stock Option Plan (incorporated herein by reference to Exhibit 99.4 in Jazz Pharmaceuticals plc's registration statement on Form S-8 (File No. 333-179075), as filed with the SEC on January 18, 2012).
10.31B+	Form of Non-U.S. Option Grant Notice and Form of Non-U.S. Option Agreement under the Jazz Pharmaceuticals plc Amended and Restated 2007 Non-Employee Directors Stock Option Plan (incorporated herein by reference to Exhibit 10.30B in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2012, as filed with the SEC on February 26, 2013).
10.31C+	Jazz Pharmaceuticals plc Amended and Restated 2007 Non-Employee Directors Stock Option Plan - Form of Non-U.S. Option Grant Notice and Form of Non-U.S. Option Agreement (approved August 1, 2013) (incorporated herein by reference to Exhibit 10.7 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2013, as filed with the SEC on November 5, 2013).
10.31D+	Amended and Restated 2007 Non-Employee Directors Stock Award Plan (approved August 4, 2016) (incorporated herein by reference to Exhibit 10.9 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2016, as filed with the SEC on August 9, 2016).
10.31E+	Amended and Restated 2007 Non-Employee Directors Stock Award Plan (approved November 3, 2016) (incorporated herein by reference to Exhibit 10.3 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2016, as filed with the SEC on November 8, 2016).
10.31F+	Amended and Restated 2007 Non-Employee Directors Stock Award Plan (approved July 30, 2020) (incorporated herein by reference to Exhibit 10.3 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2020, as filed with the SEC on August 4, 2020).
10.31G+	Form of Non-U.S. Restricted Stock Unit Award Grant Notice and Form of Non-U.S. Restricted Stock Unit Award Agreement under the Jazz Pharmaceuticals plc Amended and Restated 2007 Non-Employee Directors Stock Award Plan (incorporated herein by reference to Exhibit 10.4 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2016, as filed with the SEC on November 8, 2016).
10.31H+	Form of Non-U.S. Option Grant Notice and Form of Non-U.S. Option Agreement under the Jazz Pharmaceuticals plc Amended and Restated Non-Employee Directors 2007 Stock Award Plan (incorporated herein by reference to Exhibit 10.5 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2016, as filed with the SEC on November 8, 2016).
10.31I+	Form of Non-U.S. Option Grant Notice and Non-U.S. Option Agreement under the Jazz Pharmaceuticals plc Amended and Restated 2007 Non-Employee Directors Stock Award Plan (incorporated herein by reference to Exhibit 10.2 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2018, as filed with the SEC on November 6, 2018).
10.31J+	Form of Non-U.S. Restricted Stock Unit Award Grant Notice and Non-U.S. Restricted Stock Unit Award Agreement under the Jazz Pharmaceuticals plc Amended and Restated 2007 Non-Employee Directors Stock Award Plan (incorporated herein by reference to Exhibit 10.3 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2018, as filed with the SEC on November 6, 2018).

10.31K+	Form of Non-U.S. Option Grant Notice and Non-U.S. Option Agreement under the Jazz Pharmaceuticals plc Amended and Restated 2007 Non-Employee Directors Stock Award Plan (incorporated herein by reference to Exhibit 10.2 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended March 31, 2019, as filed with the SEC on May 7, 2019).
10.31L+	Form of Non-U.S. Restricted Stock Unit Award Grant Notice and Non-U.S. Restricted Stock Unit Award Agreement under the Jazz Pharmaceuticals plc Amended and Restated 2007 Non-Employee Directors Stock Award Plan (incorporated herein by reference to Exhibit 10.3 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended March 31, 2019, as filed with the SEC on May 7, 2019).
10.31M+	Form of Non-U.S. Option Grant Notice and Non-U.S. Option Agreement under the Jazz Pharmaceuticals plc Amended and Restated 2007 Non-Employee Directors Stock Award Plan (incorporated herein by reference to Exhibit 10.2 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2020, as filed with the SEC on November 2, 2020).
10.31N+	Form of Non-U.S. Restricted Stock Unit Award Grant Notice and Non-U.S. Restricted Stock Unit Award Agreement under the Jazz Pharmaceuticals plc Amended and Restated 2007 Non-Employee Directors Stock Award Plan (incorporated herein by reference to Exhibit 10.3 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2020, as filed with the SEC on November 2, 2020).
10.32A+	GW Pharmaceuticals plc 2020 Long-Term Incentive Plan (incorporated herein by reference to Exhibit 4.1 in GW's Registration Statement on Form S-8 (file no. 333-238737), filed with the SEC on May 27, 2020).
10.32B+	Form of Restricted Stock Unit Award Agreement under the GW Pharmaceuticals plc 2020 Long-Term Incentive Plan (incorporated herein by reference to Exhibit 10.10B in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2021, as filed with the SEC on August 3, 2021).
10.32C+	Form of Replacement Stock Option Award Agreement under the GW Pharmaceuticals plc 2020 Long-Term Incentive Plan (incorporated herein by reference to Exhibit 10.10C in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2021, as filed with the SEC on August 3, 2021).
10.32D+	Form of Replacement Restricted Stock Unit Award Agreement under the GW Pharmaceuticals plc 2020 Long-Term Incentive Plan (incorporated herein by reference to Exhibit 10.10D in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2021, as filed with the SEC on August 3, 2021).
10.33A+	Jazz Pharmaceuticals plc 2007 Employee Stock Purchase Plan, as amended and restated (incorporated herein by reference to Exhibit 10.31A in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2012, as filed with the SEC on February 26, 2013).
10.33B+	Jazz Pharmaceuticals plc 2007 Employee Stock Purchase Plan Sub-Plan Governing Purchase Rights to Participants in the Republic of Ireland (incorporated herein by reference to Exhibit 10.14C in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended March 31, 2012, as filed with the SEC on May 8, 2012).
10.34A+	Jazz Pharmaceuticals plc Cash Bonus Plan for U.S. Affiliates (approved October 30, 2019) (incorporated herein by reference to Exhibit 10.34C in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2019, as filed with the SEC on February 25, 2020).
10.34B+	Jazz Pharmaceuticals Cash Bonus Plan (Ireland and Other Specified Affiliates) (Calendar Year 2020) (incorporated herein by reference to Exhibit 10.34D in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2019, as filed with the SEC on February 25, 2020).
10.34C+	Jazz Pharmaceuticals plc Cash Bonus Plan for U.S. Affiliates (approved October 30, 2020) (incorporated herein by reference to Exhibit 10.33C in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2020, as filed with the SEC on February 23, 2021).
10.34D+	Jazz Pharmaceuticals Cash Bonus Plan (Ireland and Other Specified Affiliates) (Calendar Year 2021) (incorporated herein by reference to Exhibit 10.33D in Jazz Pharmaceuticals plc's Annual Report on Form 10-K (File No. 001-33500) for the period ended December 31, 2020, as filed with the SEC on February 23, 2021).
10.34E+	Jazz Pharmaceuticals plc Global Cash Bonus Plan (approved November, 2021).

10.35+	Amended and Restated Executive Change in Control and Severance Benefit Plan, dated as of July 31, 2019 (incorporated herein by reference to Exhibit 10.5 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2019, as filed with the SEC on November 5, 2019).
10.36A+	Amended and Restated Non-Employee Director Compensation Policy (approved May 3, 2018) (incorporated herein by reference to Exhibit 10.1 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2018, as filed with the SEC on August 7, 2018).
10.36B+	Amended and Restated Non-Employee Director Compensation Policy (approved July 21, 2020) (incorporated herein by reference to Exhibit 10.1 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended September 30, 2020, as filed with the SEC on November 2, 2020).
10.36C+	Amended and Restated Non-Employee Director Compensation Policy (approved July 29, 2021) (incorporated herein by reference to Exhibit 10.11 in Jazz Pharmaceuticals plc's Quarterly Report on Form 10-Q (File No. 001-33500) for the period ended June 30, 2021, as filed with the SEC on August 3, 2021).
21.1	Subsidiaries of Jazz Pharmaceuticals plc.
23.1	Consent of KPMG, Independent Registered Public Accounting Firm.
24.1	Power of Attorney (included on the signature page hereto).
31.1	Certification of Principal Executive Officer pursuant to Rules 13a-14(a) and 15d-14(a) promulgated under the Securities Exchange Act of 1934, as amended.
31.2	Certification of Principal Financial Officer pursuant to Rules 13a-14(a) and 15d-14(a) promulgated under the Securities Exchange Act of 1934, as amended.
32.1*	Certification of Principal Executive Officer and Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101.INS	XBRL Instance Document - The instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document
101.SCH	Inline XBRL Taxonomy Extension Schema Document
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	Inline XBRL Taxonomy Extension Labels Linkbase Document
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101)

+ Indicates management contract or compensatory plan.

† Confidential treatment has been granted for portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

‡ Certain portions of this exhibit have been omitted pursuant to Item 601(b)(2) of Regulation S-K.

* The certifications attached as Exhibit 32.1 accompany this Annual Report on Form 10-K pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, and shall not be deemed "filed" by the Registrant for purposes of Section 18 of the Securities Exchange Act of 1934, as amended.

Item 16. Form 10-K Summary

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Date: March 1, 2022

Jazz Pharmaceuticals public limited company
(Registrant)

/s/ BRUCE C. COZADD

Bruce C. Cozadd
Chairman and Chief Executive Officer and Director
(Principal Executive Officer)

/s/ RENÉE GALÁ

Renée Galá
Executive Vice President and Chief Financial Officer
(Principal Financial Officer)

/s/ PATRICIA CARR

Patricia Carr
Senior Vice President, Chief Accounting Officer
(Principal Accounting Officer)

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Bruce C. Cozadd, Renée Galá, Neena M. Patil and Patricia Carr, and each of them, as his or her true and lawful attorneys-in-fact and agents, with full power of substitution for him or her, and in his or her name in any and all capacities, to sign any and all amendments to this Annual Report on Form 10-K, and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, and any of them, his or her substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, the following persons on behalf of the registrant and in the capacities and on the dates indicated have signed this report below:

Signature	Title	Date
/s/ BRUCE C. COZADD **Bruce C. Cozadd**	Chairman, Chief Executive Officer and Director *(Principal Executive Officer)*	March 1, 2022
/s/ RENÉE GALÁ **Renée Galá**	Executive Vice President and Chief Financial Officer *(Principal Financial Officer)*	March 1, 2022
/s/ PATRICIA CARR **Patricia Carr**	Senior Vice President, Chief Accounting Officer *(Principal Accounting Officer)*	March 1, 2022
/s/ JENNIFER E. COOK **Jennifer E. Cook**	Director	March 1, 2022
/s/ PATRICK G. ENRIGHT **Patrick G. Enright**	Director	March 1, 2022
/s/ PETER GRAY **Peter Gray**	Director	March 1, 2022
/s/ HEATHER ANN MCSHARRY **Heather Ann McSharry**	Director	March 1, 2022
/s/ SEAMUS C. MULLIGAN **Seamus C. Mulligan**	Director	March 1, 2022
/s/ KENNETH W. O'KEEFE **Kenneth W. O'Keefe**	Director	March 1, 2022
/s/ ANNE O'RIORDAN **Anne O'Riordan**	Director	March 1, 2022
/s/ NORBERT G. RIEDEL, PH.D. **Norbert G. Riedel, Ph.D.**	Director	March 1, 2022
/s/ MARK D. SMITH, M.D. **Mark D. Smith, M.D.**	Director	March 1, 2022
/s/ CATHERINE A. SOHN, PHARM.D. **Catherine A. Sohn, Pharm.D.**	Director	March 1, 2022
/s/ RICK E WINNINGHAM **Rick E Winningham**	Director	March 1, 2022

Report of Independent Registered Public Accounting Firm

To the Shareholders and Board of Directors
Jazz Pharmaceuticals plc:

Opinion on the Consolidated Financial Statements

We have audited the accompanying consolidated balance sheets of Jazz Pharmaceuticals plc and subsidiaries (the 'Company') as of December 31, 2021 and 2020, the related consolidated statements of income (loss), comprehensive income (loss), stockholders' equity, and cash flows for each of the years in the three-year period ended December 31, 2021, and the related notes and financial statement schedules at Item 15(a)2 (collectively, 'the consolidated financial statements'). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2021 and 2020, and the results of its operations and its cash flows for each of the years in the three-year period ended December 31, 2021, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2021, based on criteria established in *Internal Control - Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission and our report dated March 1, 2022 expressed an unqualified opinion on the effectiveness of the Company's internal control over financial reporting.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matters

The critical audit matters communicated below are matters arising from the current period audit of the consolidated financial statements that were communicated or required to be communicated to the audit committee and that: (1) relate to accounts or disclosures that are material to the consolidated financial statements and (2) involved our especially challenging, subjective, or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matters below, providing separate opinions on the critical audit matters or on the accounts or disclosures to which they relate.

Preliminary measurement of fair value of acquired developed technology assets related to a business combination

As discussed in Note 3 to the consolidated financial statements, on May 5, 2021, the Company acquired GW Pharmaceuticals plc ('GW') in a business combination for a purchase price of $7,190.7 million. In allocating the purchase price, the Company recognized intangible assets at fair value in the amount of $5,640.0 million, including acquired developed technology of $5,480.0 million.

We identified the assessment of the preliminary measurement of fair value of acquired developed technology assets acquired in the GW Acquisition as a critical audit matter. A high degree of auditor judgment was required in evaluating the key fair value assumptions, specifically revenue forecasts. Changes to these assumptions could have a significant effect on the initial measurement of fair value.

The following are the primary procedures we performed to address this critical audit matter:

- We evaluated the design and tested the operating effectiveness of certain internal controls related to the business combinations process, including the control over the development of the key assumptions;

– We evaluated the reasonableness of the Company's revenue forecasts by comparing certain underlying assumptions to (1) company-specific operational information and management's communications to the Board of Directors and (2) available industry or other third-party reports or data.

/s/ KPMG

We have served as the Company's auditor since 2012.

Dublin, Ireland
March 1, 2022

JAZZ PHARMACEUTICALS PLC

CONSOLIDATED BALANCE SHEETS
(In thousands, except per share amounts)

	December 31, 2021	December 31, 2020
ASSETS		
Current assets:		
Cash and cash equivalents	$ 591,448	$ 1,057,769
Investments	—	1,075,000
Accounts receivable, net of allowances of $13,813 and $5,487 at December 31, 2021 and 2020, respectively	563,360	396,490
Inventories	1,072,721	95,396
Prepaid expenses	131,413	62,422
Other current assets	252,392	152,491
Total current assets	2,611,334	2,839,568
Property, plant and equipment, net	256,837	127,935
Operating lease assets	86,586	129,169
Intangible assets, net	7,152,328	2,195,051
Goodwill	1,827,609	958,303
Deferred tax assets, net	311,103	254,916
Deferred financing costs	12,029	5,238
Other non-current assets	40,813	25,721
Total assets	$ 12,298,639	$ 6,535,901
LIABILITIES AND SHAREHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 100,298	$ 26,945
Accrued liabilities	666,304	352,732
Current portion of long-term debt	31,000	246,322
Income taxes payable	9,608	25,200
Deferred revenue	2,093	2,546
Total current liabilities	809,303	653,745
Deferred revenue, non-current	463	2,315
Long-term debt, less current portion	6,018,943	1,848,516
Operating lease liabilities, less current portion	87,200	140,035
Deferred tax liabilities, net	1,300,541	130,397
Other non-current liabilities	116,998	101,148
Commitments and contingencies (Note 14)		
Shareholders' equity:		
Ordinary shares, nominal value $0.0001 per share; 300,000 shares authorized; 61,633 and 56,171 shares issued and outstanding at December 31, 2021 and 2020, respectively	6	6
Non-voting euro deferred shares, €0.01 par value per share; 4,000 shares authorized, issued and outstanding at both December 31, 2021 and 2020	55	55
Capital redemption reserve	472	472
Additional paid-in capital	3,534,792	2,633,670
Accumulated other comprehensive loss	(400,360)	(134,352)
Retained earnings	830,226	1,159,894
Total shareholders' equity	3,965,191	3,659,745
Total liabilities and shareholders' equity	$ 12,298,639	$ 6,535,901

The accompanying notes are an integral part of these consolidated financial statements.

JAZZ PHARMACEUTICALS PLC

CONSOLIDATED STATEMENTS OF INCOME (LOSS)
(In thousands, except per share amounts)

	Year Ended December 31,		
	2021	2020	2019
Revenues:			
Product sales, net	$ 3,079,001	$ 2,346,660	$ 2,135,601
Royalties and contract revenues	15,237	16,907	26,160
Total revenues	3,094,238	2,363,567	2,161,761
Operating expenses:			
Cost of product sales (excluding amortization of acquired developed technologies)	440,760	148,917	127,930
Selling, general and administrative	1,451,683	854,233	736,942
Research and development	505,748	335,375	299,726
Intangible asset amortization	525,769	259,580	354,814
Impairment charge	—	136,139	—
Acquired in-process research and development	—	251,250	109,975
Total operating expenses	2,923,960	1,985,494	1,629,387
Income from operations	170,278	378,073	532,374
Interest expense, net	(278,766)	(99,707)	(72,261)
Foreign exchange loss	(4,350)	(3,271)	(5,811)
Income (loss) before income tax expense (benefit) and equity in loss of investees	(112,838)	275,095	454,302
Income tax expense (benefit)	216,116	33,517	(73,154)
Equity in loss of investees	714	2,962	4,089
Net income (loss)	$ (329,668)	$ 238,616	$ 523,367
Net income (loss) per ordinary share:			
Basic	$ (5.52)	$ 4.28	$ 9.22
Diluted	$ (5.52)	$ 4.22	$ 9.09
Weighted-average ordinary shares used in per share calculations - basic	59,694	55,712	56,749
Weighted-average ordinary shares used in per share calculations - diluted	59,694	56,517	57,550

The accompanying notes are an integral part of these consolidated financial statements.

JAZZ PHARMACEUTICALS PLC

CONSOLIDATED STATEMENTS OF COMPREHENSIVE INCOME (LOSS)

(In thousands)

	Year Ended December 31,		
	2021	2020	2019
Net income (loss)	$ (329,668)	$ 238,616	$ 523,367
Other comprehensive income (loss):			
Foreign currency translation adjustments	(268,347)	90,183	(20,720)
Unrealized gain (loss) on cash flow hedging activities, net of income tax expense (benefit) of $353, ($163) and ($697), respectively	2,468	(1,142)	(4,882)
Unrealized loss on fair value hedging activities, net of income tax benefit of $43, $— and $—, respectively	(129)	—	—
Other comprehensive income (loss)	(266,008)	89,041	(25,602)
Total comprehensive income (loss)	$ (595,676)	$ 327,657	$ 497,765

The accompanying notes are an integral part of these consolidated financial statements.

JAZZ PHARMACEUTICALS PLC

CONSOLIDATED STATEMENTS OF SHAREHOLDERS' EQUITY
(In thousands)

	Ordinary Shares		Non-voting Euro Deferred		Capital Redemption Reserve	Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Retained Earnings	Total Equity
	Shares	Amount	Shares	Amount					
Balance at December 31, 2018	57,504	$ 6	4,000	$ 55	$ 472	$ 2,113,630	$ (197,791)	$ 841,050	$ 2,757,422
Cumulative effect adjustment from adoption of new accounting standards	—	—	—	—	—	—	—	4,848	4,848
Issuance of ordinary shares in conjunction with exercise of share options	515	—	—	—	—	46,477	—	—	46,477
Issuance of ordinary shares under employee stock purchase plan	106	—	—	—	—	11,354	—	—	11,354
Issuance of ordinary shares in conjunction with vesting of restricted stock units	265	—	—	—	—	—	—	—	—
Shares withheld for payment of employee's withholding tax liability	—	—	—	—	—	(16,739)	—	—	(16,739)
Share-based compensation	—	—	—	—	—	111,304	—	—	111,304
Shares repurchased	(2,250)	—	—	—	—	—	—	(301,450)	(301,450)
Other comprehensive loss	—	—	—	—	—	—	(25,602)	—	(25,602)
Net income	—	—	—	—	—	—	—	523,367	523,367
Balance at December 31, 2019	56,140	6	4,000	55	472	2,266,026	(223,393)	1,067,815	3,110,981
Stock issued under directors deferred compensation plan	37	—	—	—	—	—	—	—	—
Issuance of Exchangeable Senior Notes, due 2026	—	—	—	—	—	176,260	—	—	176,260
Partial repurchase of Exchangeable Senior Notes, due 2021	—	—	—	—	—	(12,513)	—	—	(12,513)
Issuance of ordinary shares in conjunction with exercise of share options	780	—	—	—	—	86,984	—	—	86,984
Issuance of ordinary shares under employee stock purchase plan	125	—	—	—	—	12,697	—	—	12,697
Issuance of ordinary shares in conjunction with vesting of restricted stock units	290	—	—	—	—	—	—	—	—
Shares withheld for payment of employee's withholding tax liability	—	—	—	—	—	(16,877)	—	—	(16,877)
Share-based compensation	—	—	—	—	—	121,093	—	—	121,093
Shares repurchased	(1,201)	—	—	—	—	—	—	(146,537)	(146,537)
Other comprehensive income	—	—	—	—	—	—	89,041	—	89,041
Net income	—	—	—	—	—	—	—	238,616	238,616
Balance at December 31, 2020	56,171	$ 6	4,000	$ 55	$ 472	$ 2,633,670	$ (134,352)	$ 1,159,894	$ 3,659,745

JAZZ PHARMACEUTICALS PLC

CONSOLIDATED STATEMENTS OF SHAREHOLDERS' EQUITY—(Continued)
(In thousands)

	Ordinary Shares		Non-voting Euro Deferred		Capital Redemption Reserve	Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Retained Earnings	Total Equity
	Shares	Amount	Shares	Amount					
Balance at December 31, 2020	56,171	$ 6	4,000	$ 55	$ 472	$ 2,633,670	$ (134,352)	$ 1,159,894	$ 3,659,745
Issuance of ordinary shares in connection with the acquisition of GW Pharmaceuticals plc	3,798	—	—	—	—	608,456	—	—	608,456
Share-based payment - precombination service in connection with the acquisition of GW Pharmaceuticals plc	—	—	—	—	—	3,555	—	—	3,555
Issuance of ordinary shares in conjunction with exercise of share options	1,042	—	—	—	—	119,058	—	—	119,058
Issuance of ordinary shares under employee stock purchase plan	157	—	—	—	—	16,203	—	—	16,203
Issuance of ordinary shares in conjunction with vesting of restricted stock units	465	—	—	—	—	—	—	—	—
Shares withheld for payment of employee's withholding tax liability	—	—	—	—	—	(35,602)	—	—	(35,602)
Share-based compensation	—	—	—	—	—	189,452	—	—	189,452
Other comprehensive loss	—	—	—	—	—	—	(266,008)	—	(266,008)
Net loss	—	—	—	—	—	—	—	(329,668)	(329,668)
Balance at December 31, 2021	61,633	$ 6	4,000	$ 55	$ 472	$ 3,534,792	$ (400,360)	$ 830,226	$ 3,965,191

The accompanying notes are an integral part of these consolidated financial statements.

JAZZ PHARMACEUTICALS PLC

CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	Year Ended December 31,		
	2021	2020	2019
Operating activities			
Net income (loss)	$ (329,668)	$ 238,616	$ 523,367
Adjustments to reconcile net income (loss) to net cash provided by operating activities:			
Intangible asset amortization	525,769	259,580	354,814
Acquisition accounting inventory fair value step-up adjustment	223,085	—	—
Share-based compensation	189,006	120,998	110,563
Non-cash interest expense	92,655	61,748	46,396
Deferred tax expense (benefit)	69,198	(136,937)	(236,610)
Depreciation	26,714	18,673	15,342
Provision for losses on accounts receivable and inventory	19,668	15,000	6,668
Impairment charge	—	136,139	—
Acquired in-process research and development	—	251,250	109,975
Other non-cash transactions	10,032	14,580	59
Distributions from equity method investees	—	5,438	—
Changes in assets and liabilities:			
Accounts receivable	(92,735)	(38,647)	(92,326)
Inventories	(48,861)	(30,537)	(32,790)
Prepaid expenses and other current assets	(83,320)	(98,042)	(25,650)
Operating lease assets	15,583	12,366	14,148
Other non-current assets	817	21,913	(18,919)
Accounts payable	57,021	(18,935)	4,770
Accrued liabilities	142,355	79,477	(5,565)
Income taxes payable	(15,524)	13,038	10,056
Deferred revenue	(2,305)	(4,720)	(5,414)
Operating lease liabilities, less current portion	(16,037)	(12,383)	(6,044)
Other non-current liabilities	(4,946)	(8,967)	3,561
Net cash provided by operating activities	778,507	899,648	776,401
Investing activities			
Proceeds from maturity of investments	1,095,000	1,755,000	985,000
Purchases of property, plant and equipment	(27,641)	(15,004)	(40,135)
Acquisition of intangible assets	(17,891)	(113,000)	(80,500)
Acquisition of investments	(26,819)	(2,397,675)	(917,100)
Acquisition of a business, net of cash acquired	(6,234,792)	—	—
Acquired in-process research and development	—	(251,250)	(61,700)
Asset acquisition, net of cash acquired	—	—	(55,074)
Net proceeds from sale of assets	—	14,259	14,209
Net cash used in investing activities	(5,212,143)	(1,007,670)	(155,300)
Financing activities			
Net proceeds from issuance of borrowings under credit agreement	3,719,930	—	—
Net proceeds from issuance of Senior Secured Notes, due 2029	1,471,533	—	—
Proceeds from employee equity incentive and purchase plans	135,261	99,681	57,831
Payment of employee withholding taxes related to share-based awards	(35,602)	(16,877)	(16,739)
Payments for repurchase of Exchangeable Senior Notes, due 2021	(218,812)	(356,188)	—
Repayments of long-term debt	(1,101,788)	(33,387)	(33,387)
Net proceeds from issuance of Exchangeable Senior Notes, due 2026	—	981,381	—
Net proceeds from revolving credit facility	—	500,000	—
Share repurchases	—	(146,537)	(301,450)
Repayments under revolving credit facility	—	(500,000)	—
Net cash provided by (used in) financing activities	3,970,522	528,073	(293,745)
Effect of exchange rates on cash and cash equivalents	(3,207)	374	366
Net increase (decrease) in cash and cash equivalents	(466,321)	420,425	327,722
Cash and cash equivalents, at beginning of period	1,057,769	637,344	309,622
Cash and cash equivalents, at end of period	$ 591,448	$ 1,057,769	$ 637,344

JAZZ PHARMACEUTICALS PLC

CONSOLIDATED STATEMENTS OF CASH FLOWS—(Continued)
(In thousands)

	Year Ended December 31,		
	2021	2020	2019
Supplemental disclosure of cash flow information:			
Cash paid for interest	$ 138,271	$ 42,470	$ 43,002
Cash paid for income taxes, net of refunds	271,217	226,823	183,610

The accompanying notes are an integral part of these consolidated financial statements.

JAZZ PHARMACEUTICALS PLC

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. Organization and Description of Business

Jazz Pharmaceuticals plc is a global biopharmaceutical company whose purpose is to innovate to transform the lives of patients and their families. We are dedicated to developing life-changing medicines for people with serious diseases - often with limited or no therapeutic options. We have a diverse portfolio of marketed medicines and novel product candidates, from early- to late-stage development, in neuroscience and oncology. Within these therapeutic areas, we strive to identify new options for patients by actively exploring small molecules and biologics, and through innovative delivery technologies and cannabinoid science.

Our lead marketed products are:

Neuroscience

- **Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution**, a product approved by the U.S. Food and Drug Administration, or FDA, in July 2020 and launched in the U.S. in November 2020 for the treatment of cataplexy or excessive daytime sleepiness, or EDS, in patients with narcolepsy aged seven years of age and older, and also approved by FDA in August 2021 for the treatment of idiopathic hypersomnia, or IH, in adults and launched in the U.S. in November 2021. Xywav contains 92% less sodium than Xyrem®;
- **Xyrem (sodium oxybate) oral solution**, a product approved by FDA and distributed in the U.S. for the treatment of both cataplexy and EDS in patients seven years of age and older with narcolepsy; Jazz also markets Xyrem in Canada for the treatment of cataplexy in patients with narcolepsy. Xyrem is also approved and distributed in Europe, Great Britain and other markets through a licensing agreement;
- **Epidiolex® (cannabidiol) oral solution**, a product approved by FDA and launched in the U.S. in 2018 by GW Pharmaceuticals plc, or GW, and currently indicated for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients one year of age or older; in Europe (where it is marketed as Epidyolex®) and other markets, it is approved for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome, in conjunction with clobazam (EU and Great Britain only), in patients 2 years of age and older and for adjunctive treatment of seizures associated with tuberous sclerosis complex in patients 2 years of age and older;
- **Sunosi® (solriamfetol)**, a product approved by FDA and marketed in the U.S., Canada, Europe and Great Britain to improve wakefulness in adult patients with EDS associated with narcolepsy or obstructive sleep apnea; and
- **Sativex® (nabiximols) oral solution**, a product approved and marketed in the U.K., Canada and other markets as treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis, or MS, who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy.

Oncology

- **Zepzelca® (lurbinectedin)**, a product approved by FDA in June 2020 and launched in the U.S. in July 2020 for the treatment of adult patients with metastatic small cell lung cancer, or SCLC, with disease progression on or after platinum-based chemotherapy; in Canada, Zepzelca was approved in September 2021 for the treatment of adults with Stage III or metastatic SCLC, who have progressed on or after platinum-containing therapy;
- **Rylaze™** (recombinant Erwinia asparaginase), a product approved by FDA in June 2021 and launched in the U.S. in July 2021 for use as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia, or ALL, or lymphoblastic lymphoma, or LBL, in adults and pediatric patients who have developed hypersensitivity to *E. coli*-derived asparaginase;
- **Vyxeos® (daunorubicin and cytarabine) liposome for injection**, a product approved in the U.S., Canada, Europe and Great Britain (marketed as Vyxeos® liposomal in Europe and Great Britain) for the treatment of adults with newly-diagnosed therapy-related acute myeloid leukemia, or t-AML, or AML with myelodysplasia-related changes (AML-MRC). An expanded indication was granted in the U.S. for the treatment of newly diagnosed t-AML or AML-MRC in pediatric patients aged 1 year and older; and

- **Defitelio® (defibrotide sodium)**, is a product approved in the U.S. and Brazil for the treatment of hepatic veno-occlusive disease, or VOD, with renal or pulmonary dysfunction following hematopoietic stem cell transplantation, or HSCT, and in Japan for the treatment of hepatic sinusoidal obstruction syndrome (hepatic-veno occlusive disease). It is currently approved in the EU, Great Britain, Canada, Israel, South Korea, Australia and Switzerland for the treatment of severe hepatic VOD, also known as sinusoidal obstructive syndrome, or SOS, in HSCT therapy. It is indicated in adults and pediatric patients over 1 month of age.

In May 2021, we acquired GW Pharmaceuticals plc, or GW, with the objectives of broadening our neuroscience portfolio, further diversifying our revenue and driving sustainable, long-term value creation opportunities. The total consideration paid by us for the entire issued share capital of GW was $7.2 billion. The acquisition, which we refer to as the GW Acquisition, closed on May 5, 2021. For further information regarding the GW Acquisition, please see Note 3.

Throughout this report, unless otherwise indicated or the context otherwise requires, all references to “Jazz Pharmaceuticals,” “the registrant,” "the Company", “we,” “us,” and “our” refer to Jazz Pharmaceuticals plc and its consolidated subsidiaries. Throughout this report, all references to “ordinary shares” refer to Jazz Pharmaceuticals plc’s ordinary shares.

2. Summary of Significant Accounting Policies

Basis of Presentation

The consolidated financial statements have been prepared in accordance with U.S. generally accepted accounting principles, or U.S. GAAP, and include the accounts of Jazz Pharmaceuticals plc and our subsidiaries and intercompany transactions and balances have been eliminated. Our consolidated financial statements include the results of operations of businesses we have acquired from the date of each acquisition for the applicable reporting periods.

The results of operations of the acquired GW business, along with the estimated fair values of the assets acquired and liabilities assumed in the GW Acquisition, have been included in our consolidated financial statements since the closing of the GW Acquisition on May 5, 2021.

Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets, liabilities, revenues and expenses, and related disclosures in the consolidated financial statements and accompanying notes. Management bases its estimates on historical experience and on assumptions believed to be reasonable under the circumstances. Actual results could differ materially from those estimates.

Adoption of New Accounting Standards

In December 2019, the Financial Accounting Standards Board, or FASB, issued ASU No. 2019-12, "Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes", which simplifies the accounting for income taxes by removing certain exceptions to the general principles in the existing guidance for income taxes and making other minor improvements. We adopted this standard on January 1, 2021 and adoption did not have a material impact on our consolidated financial statements.

Significant Risks and Uncertainties

We have implemented a comprehensive response strategy designed to manage the ongoing impact of the COVID-19 pandemic on our employees, patients and our business. The prolonged nature of the pandemic is negatively impacting our business in a varied manner due to the emergence of the Delta and Omicron variants and other variants with increased transmissibility, even in some cases in vaccinated people, limited access to health care provider offices and institutions and the willingness of patients or parents of patients to seek treatment. We expect that our business, financial condition, results of operations and growth prospects may continue to be negatively impacted by the pandemic on a limited basis that may vary depending on the context. However we have begun to observe, and expect to continue to observe, a gradual normalization in patient and healthcare provider practices, as providers and patients have adapted their behaviors and procedures to the evolving circumstances and as COVID-19 vaccines continue to be administered. With respect to our commercialization activities, while there continues to be some negative impact on demand, new patient starts and treatments for our products arising from the pandemic, primarily due to the inherent limitations of telemedicine and a reprioritization of healthcare resources toward COVID-19, we have seen improvements as healthcare systems have adapted to cope with the ongoing situation. We believe these dynamics have negatively impacted new patient starts in the U.S. and Europe. The extent of the impact on our ability to generate sales of approved products, execute on new product launches, our clinical development and regulatory efforts, our corporate development objectives and the value of and market for our ordinary shares, will depend on future developments that are highly uncertain and cannot be predicted with confidence at this time. Such developments include continued spread of the

Delta and Omicron variants in the U.S. and other countries and the potential emergence of other SARS-CoV-2 variants that may prove especially contagious or virulent, the ultimate duration and severity of the pandemic, governmental "stay-at-home" orders and travel restrictions, quarantines, social distancing and business closure requirements in the U.S., Ireland and other countries, and the effectiveness of vaccination programs and other actions taken globally to contain and treat the disease.

Our business has been substantially dependent on Xyrem and while we expect that our business will continue to be substantially dependent on oxybate product sales from both Xywav and Xyrem, there is no guarantee that we can maintain oxybate revenues at or near current levels, or that oxybate revenues will continue to grow. Our ability to maintain or increase oxybate revenues and realize the anticipated benefits from our investment in Xywav are subject to a number of risks and uncertainties including, without limitation, those related to the launch of Xywav for the treatment of idiopathic hypersomnia in adults and adoption in that indication; competition from the introduction of authorized generic and generic versions of sodium oxybate and new products for treatment of cataplexy and/or EDS in narcolepsy in the U.S. market and from other competitors; the current and potential impacts of the COVID-19 pandemic, including the current and expected future negative impact on demand for our products; increased pricing pressure from, changes in policies by, or restrictions on reimbursement imposed by, third party payors, including our ability to maintain adequate coverage and reimbursement for Xywav; increased rebates required to maintain access to our products; challenges to our intellectual property around Xyrem and/or Xywav, including pending antitrust and intellectual property litigation; and continued acceptance of Xywav and Xyrem by physicians and patients.

In addition to risks related specifically to Xywav and Xyrem, we are subject to other challenges and risks related to successfully commercializing a portfolio of oncology products and other neuroscience products, including Epidiolex, Sunosi, Defitelio, Vyxeos, Rylaze and Zepzelca, and other risks specific to our business and our ability to execute on our strategy, as well as risks and uncertainties common to companies in the pharmaceutical industry with development and commercial operations, including, without limitation, risks and uncertainties associated with: ongoing clinical research activity and related outcomes, obtaining regulatory approval of our late-stage product candidates; effectively commercializing our recently approved or acquired products such as Xywav, Epidiolex, Zepzelca and Rylaze; obtaining and maintaining adequate coverage and reimbursement for our products; contracting and rebates to pharmacy benefit managers that reduces our net revenue; increasing scrutiny of pharmaceutical product pricing and resulting changes in healthcare laws and policy; market acceptance; regulatory concerns with controlled substances generally and the potential for abuse; future legislation, Drug enforcement agency, or DEA, action or FDA action authorizing the sale, distribution, use, and insurance reimbursement of non-FDA approved cannabinoid products; delays or problems in the supply of our products, loss of single source suppliers or failure to comply with manufacturing regulations; delays or problems with third parties that are part of our manufacturing and supply chain; identifying, acquiring or in-licensing additional products or product candidates; pharmaceutical product development and the inherent uncertainty of clinical success; the challenges of protecting and enhancing our intellectual property rights; complying with applicable regulatory requirements; and possible restrictions on our ability and flexibility to pursue certain future opportunities as a result of our substantial outstanding debt obligations. In addition, the success of the GW Acquisition will depend, in part, on our ability to realize the anticipated benefits from successfully combining our and GW's historical businesses and the integration of our business practices and operations with GW's so that we can fully realize the anticipated benefits of the acquisition. The anticipated benefits to us of the GW Acquisition may not be realized fully within the expected timeframe or at all or may take longer to realize or cost more than expected, which could materially and adversely affect our business, financial condition, results of operations and growth prospects. Moreover, to the extent the COVID-19 pandemic continues to adversely affect our business and results of operations, it may also have the effect of heightening many of the other risks and uncertainties discussed above.

Concentrations of Risk

Financial instruments that potentially subject us to concentrations of credit risk consist of cash, cash equivalents, investments and derivative contracts. Our investment policy permits investments in U.S. federal government and federal agency securities, corporate bonds or commercial paper issued by U.S. corporations, money market instruments, certain qualifying money market mutual funds, certain repurchase agreements, and tax-exempt obligations of U.S. states, agencies and municipalities and places restrictions on credit ratings, maturities, and concentration by type and issuer. We are exposed to credit risk in the event of a default by the financial institutions holding our cash, cash equivalents and investments to the extent recorded on the balance sheet.

We manage our foreign currency transaction risk and interest rate risk within specified guidelines through the use of derivatives. All of our derivative instruments are utilized for risk management purposes, and we do not use derivatives for speculative trading purposes. As of December 31, 2021 and 2020, we had foreign exchange forward contracts with notional amounts totaling $347.2 million and $357.4 million, respectively. As of December 31, 2021 and 2020, the outstanding foreign exchange forward contracts had a net liability fair value of $2.6 million and a net asset fair value of $11.1 million, respectively.

As of December 31, 2021, we had a cross-currency interest rate swap with a notional amount of $251.0 million. This outstanding cross-currency interest rate swap contract had a net liability fair value of $15.2 million as of December 31, 2021. The counterparties to these contracts are large multinational commercial banks, and we believe the risk of nonperformance is not significant.

We are also subject to credit risk from our accounts receivable related to our product sales. We monitor our exposure within accounts receivable and record a reserve against uncollectible accounts receivable as necessary. We extend credit to pharmaceutical wholesale distributors and specialty pharmaceutical distribution companies, primarily in the U.S., and to other international distributors and hospitals. Customer creditworthiness is monitored and collateral is not required. We monitor economic conditions in certain European countries which may result in variability of the timing of cash receipts and an increase in the average length of time that it takes to collect accounts receivable outstanding. Historically, we have not experienced significant credit losses on our accounts receivable and as of December 31, 2021, allowances on receivables were not material. As of December 31, 2021, three customers accounted for 74% of gross accounts receivable, Express Scripts Specialty Distribution Services, Inc. and its affiliates, or ESSDS, which accounted for 52% of gross accounts receivable, McKesson Corporation and affiliates, or McKesson, which accounted for 12% of gross accounts receivable and Cardinal Health Inc., or Cardinal, which accounted for 10% of gross accounts receivable. As of December 31, 2020, three customers accounted for 84% of gross accounts receivable, ESSDS, which accounted for 68% of gross accounts receivable, McKesson, which accounted for 12% of gross accounts receivable and Cardinal which accounted for 4% of gross accounts receivable.

We depend on single source suppliers for most of our products, product candidates and their active pharmaceutical ingredients, or APIs. With respect to our oxybate products, the API is manufactured for us by a single source supplier and the finished product are manufactured both by us in our facility in Athlone, Ireland and by our U.S.-based supplier.

Business Acquisitions

Our consolidated financial statements include the results of operations of an acquired business from the date of acquisition. We account for acquired businesses using the acquisition method of accounting. The acquisition method of accounting for acquired businesses requires, among other things, that assets acquired, liabilities assumed and any noncontrolling interests in the acquired business be recognized at their estimated fair values as of the acquisition date, with limited exceptions, and that the fair value of acquired in-process research and development, or IPR&D, be recorded on the balance sheet. Also, transaction costs are expensed as incurred. Any excess of the acquisition consideration over the assigned values of the net assets acquired is recorded as goodwill. Contingent consideration is included within the acquisition cost and is recognized at its fair value on the acquisition date. A liability resulting from contingent consideration is remeasured to fair value at each reporting date until the contingency is resolved and changes in fair value are recognized in earnings.

Cash Equivalents and Investments

We consider all highly liquid investments, readily convertible to cash, that mature within three months or less from date of purchase to be cash equivalents.

Investments consist of time deposits with initial maturities of greater than three months. Collectively, cash equivalents and investments are considered available-for-sale and are recorded at fair value. Unrealized gains and losses, net of tax, are recorded in accumulated other comprehensive loss in shareholders' equity. We use the specific-identification method for calculating realized gains and losses on securities sold. Realized gains and losses and declines in value judged to be other than temporary on investments are included in interest expense, net in the consolidated statements of income (loss).

Derivative Instruments and Hedging Activities

We record the fair value of derivative instruments as either assets or liabilities on the consolidated balance sheets. Changes in the fair value of derivative instruments are recorded each period in current earnings or other comprehensive income (loss), depending on whether a derivative instrument is designated as part of a hedging transaction and, if it is, the type of hedging transaction. For a derivative to qualify as a hedge at inception and throughout the hedged period, we formally document the nature and relationships between the hedging instruments and hedged item.

For derivatives formally designated as hedges, we assess both at inception and quarterly thereafter, whether the hedging derivatives are highly effective in offsetting changes in either the fair value or cash flows of the hedged item.

Gains or losses on cash flow hedges are reclassified from other comprehensive income (loss) to earnings when the hedged transaction occurs. If we determine that a forecasted transaction is no longer probable of occurring, we discontinue hedge accounting and any related unrealized gain or loss on the derivative instrument is recognized in current earnings.

We designate cross-currency interest rate swaps as fair value hedges to hedge foreign currency risks related to our borrowings denominated in currencies other than the U.S. dollar. Fair value hedge amounts included in the assessment of

hedge effectiveness are recognized in foreign exchange gain (loss) within the consolidated statements of income (loss), along with the offsetting gains and losses of the related hedged item. We have elected to exclude the total forward points or currency basis from the assessment of hedge effectiveness and account for them as excluded components. The initial fair value of the excluded component is amortized to foreign exchange gain (loss) and the difference between changes in fair value of the excluded component and the amount recorded in earnings is recorded in other comprehensive income (loss).

Derivatives that are not designated and do not qualify as hedges are adjusted to fair value through current earnings.

Inventories

Inventories are valued at the lower of cost or net realizable value. Cost is determined using the first-in, first-out method for all inventories. Our policy is to write down inventory that has become obsolete, inventory that has a cost basis in excess of its expected net realizable value and inventory in excess of expected requirements. The estimate of excess quantities is subjective and primarily dependent on our estimates of future demand for a particular product. If our estimate of future demand changes, we consider the impact on the reserve for excess inventory and adjust the reserve as required. Increases in the reserve are recorded as charges in cost of product sales.

We capitalize inventory costs associated with our products prior to regulatory approval when, based on management's judgment, future commercialization is considered probable and the future economic benefit is expected to be realized; otherwise, such costs are expensed as research and development. The determination to capitalize inventory costs is based on various factors, including status and expectations of the regulatory approval process, any known safety or efficacy concerns, potential labeling restrictions, and any other impediments to obtaining regulatory approval. We had no pre-approval inventory on our consolidated balance sheet as of December 31, 2021 or 2020.

Our inventory production process for our cannabinoid products includes the cultivation of botanical raw material. Because of the duration of the cultivation process, a portion of our inventory will not be sold within one year. Consistent with the practice in other industries that cultivate botanical raw materials, all inventory is classified as a current asset.

Property, Plant and Equipment

Property, plant and equipment are stated at cost, less accumulated depreciation. Depreciation is computed using the straight-line method over the estimated useful lives of the assets. Estimated useful lives are as follows:

Buildings	40 years
Manufacturing equipment and machinery	4-20 years
Computer software and equipment	3-7 years
Furniture and fixtures	5 years

Leasehold improvements are amortized over the shorter of the noncancelable term of our leases or their economic useful lives. Maintenance and repairs are expensed as incurred.

Leases

We determine if an arrangement is a lease at inception. Leases are classified at lease commencement as either operating leases or finance leases. Operating leases are included in operating lease assets, other current liabilities, and operating lease liabilities on our consolidated balance sheets. Finance lease assets are included in property, plant and equipment, net, and finance lease liabilities are included in other current liabilities and other non-current liabilities in our consolidated balance sheets. Lease assets and lease liabilities are recognized based on the present value of the future minimum lease payments over the lease term at commencement date. In determining the net present value of lease payments, we use our incremental borrowing rate based on the information available at the lease commencement date. The lease asset also includes any lease payments made, reduced by lease incentives and increased by initial direct costs incurred. Our lease terms may include options to extend or terminate the lease when it is reasonably certain that we will exercise that option. Operating lease expense for minimum lease payments is recognized on a straight-line basis over the lease term. Finance lease expense is recognized as depreciation expense of fixed assets and interest expense on finance lease liabilities.

We have lease agreements with lease and non-lease components, which are generally accounted for separately. For vehicle leases we account for the lease and non-lease components as a single lease component.

We have elected the short-term lease exemption and, therefore, do not recognize a lease asset or corresponding liability for lease arrangements with an original term of 12 months or less. Rent expense under short-term leases is recognized on a straight-line basis over the lease term.

Goodwill

Goodwill represents the excess of the acquisition consideration over the fair value of assets acquired and liabilities assumed. We have determined that we operate in a single segment and have a single reporting unit associated with the development and commercialization of pharmaceutical products. In performing the annual impairment test, the fair value of the reporting unit is compared to its corresponding carrying value, including goodwill. If the carrying value exceeds the fair value of the reporting unit an impairment loss will be recognized for the amount by which the reporting unit's carrying amount exceeds its fair value, not to exceed the carrying amount of goodwill. We test goodwill for impairment annually in October and when events or changes in circumstances indicate that the carrying value may not be recoverable.

Acquired In-Process Research and Development

The initial costs of rights to IPR&D projects acquired in an asset acquisition are expensed as IPR&D unless the project has an alternative future use. The fair value of IPR&D projects acquired in a business combination are capitalized and accounted for as indefinite-lived intangible assets until the underlying project receives regulatory approval, at which point the intangible asset will be accounted for as a finite-lived intangible asset, or discontinued, at which point the intangible asset will be written off. Development costs incurred after an acquisition are expensed as incurred.

Intangible Assets

Intangible assets with finite useful lives consist primarily of purchased developed technology and are amortized on a straight-line basis over their estimated useful lives, which range from two to twenty years. The estimated useful lives associated with finite-lived intangible assets are consistent with the estimated lives of the associated products and may be modified when circumstances warrant. Such assets are reviewed for impairment when events or circumstances indicate that the carrying value of an asset may not be recoverable. An impairment loss would be recognized when estimated undiscounted future cash flows expected to result from the use of an asset and its eventual disposition are less than its carrying amount. The amount of any impairment is measured as the difference between the carrying amount and the fair value of the impaired asset.

Revenue Recognition

Our revenue comprises product sales, net and royalty and contract revenues. Revenues are recognized when control of the promised goods or services is transferred to our customers, in an amount that reflects the consideration we expect to be entitled to in exchange for those goods or services. Prior to recognizing revenue, we make estimates of the transaction price, including variable consideration that is subject to a constraint. Amounts of variable consideration are included in the transaction price to the extent that it is probable that a significant reversal in the amount of cumulative revenue recognized will not occur when the uncertainty associated with the variable consideration is subsequently resolved.

Product Sales, Net

Product sales revenue is recognized when control has transferred to the customer, which occurs at a point in time, which is typically on delivery to the customer or, in the case of products that are subject to consignment agreements, when the customer removes product from our consigned inventory location for shipment directly to a patient.

Reserves for Variable Consideration

Revenues from sales of products are recorded at the net sales price, which includes estimates of variable consideration for which reserves are established and which relate to returns, specialty distributor fees, wholesaler fees, prompt payment discounts, government rebates, government chargebacks, coupon programs and rebates under managed care plans and commercial payor contracts. Calculating certain of these reserves involves estimates and judgments and we determine their expected value based on sales or invoice data, contractual terms, historical utilization rates, new information regarding changes in these programs' regulations and guidelines that would impact the amount of the actual rebates, our expectations regarding future utilization rates for these programs and channel inventory data. These reserves reflect our best estimates of the amount of consideration to which we are entitled based on the terms of the contract. The amount of variable consideration that is included in the transaction price may be constrained, and is included in the net sales price only to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period. We reassess our reserves for variable consideration at each reporting date. Historically, adjustments to estimates for these reserves have not been material.

Reserves for returns, specialty distributor fees, wholesaler fees, government rebates, coupon programs and rebates under managed care plans and commercial payor contracts are included within current liabilities in our consolidated balance sheets. Reserves for government chargebacks and prompt payment discounts are shown as a reduction in accounts receivable.

Royalties and Contract Revenues

We enter into out-licensing agreements under which we license certain rights to our products or product candidates to third parties. If a licensing arrangement includes multiple goods or services, we consider whether the license is distinct. If the license to our intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, we recognize revenue from non-refundable, upfront fees allocated to the license when the license is transferred to the licensee and the licensee is able to use and benefit from the license. If the license to our intellectual property is determined not to be distinct, it is combined with other goods or services into a combined performance obligation. We consider whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from non-refundable, upfront fees. We evaluate the measure of progress each reporting date and, if necessary, adjust the measure of performance and related revenue recognition.

At the inception of each arrangement that includes development milestone payments, we evaluate whether the milestones are considered probable of being reached and estimate the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within our control or that of the licensee, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. The transaction price is allocated to each performance obligation on a relative stand-alone selling price basis, for which we recognize revenue as or when the performance obligations under the contract are satisfied. At the end of each subsequent reporting period, we re-evaluate the probability of achievement of such development milestones and any related constraint, and if necessary, adjust our estimate of the overall transaction price.

For arrangements that include sales-based royalties and milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties and sales-based milestones relate, we recognize revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty or sales-based milestone has been allocated has been satisfied (or partially satisfied).

Cost of Product Sales

Cost of product sales includes manufacturing and distribution costs, the cost of drug substance, royalties due to third parties on product sales, product liability and cargo insurance, FDA user fees, freight, shipping, handling and storage costs and salaries and related costs of employees involved with production. Excluded from cost of product sales shown on the consolidated statements of income (loss) is amortization of acquired developed technology of $525.8 million, $259.6 million and $243.7 million in 2021, 2020 and 2019, respectively.

Research and Development

Research and development expenses consist primarily of costs related to clinical studies and outside services, personnel expenses and other research and development costs, including milestone payments incurred prior to regulatory approval of products. Clinical study and outside services costs relate primarily to services performed by clinical research organizations, clinical studies performed at clinical sites, materials and supplies, and other third party fees. Personnel expenses relate primarily to salaries, benefits and share-based compensation. Other research and development expenses primarily include overhead allocations consisting of various support and facilities-related costs. Research and development costs are expensed as incurred. For product candidates that have not been approved by FDA, inventory used in clinical trials is expensed at the time of production and recorded as research and development expense. For products that have been approved by FDA, inventory used in clinical trials is expensed at the time the inventory is packaged for the trial.

Advertising Expenses

We expense the costs of advertising, including promotional expenses, as incurred. Advertising expenses were $161.5 million, $99.6 million and $65.4 million in 2021, 2020 and 2019, respectively.

Income Taxes

We use the asset and liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are determined based on differences between the financial statement carrying amount and the tax basis of assets and liabilities and are measured using enacted tax rates and laws that will be in effect when the differences are expected to reverse. A valuation allowance is provided when it is more-likely-than-not that some portion or all of a deferred tax asset will not be realized. We recognize the benefits of a tax position if it is “more-likely-than-not” of being sustained. A recognized tax benefit is then measured as the largest amount of tax benefit that is greater than fifty percent likely of being realized upon settlement. Interest and penalties related to an underpayment of income taxes are included in the income tax expense and classified with the related liability on the consolidated balance sheets.

Foreign Currency

Our functional and reporting currency is the U.S. dollar. The assets and liabilities of our subsidiaries that have a functional currency other than the U.S. dollar are translated into U.S. dollars at the exchange rate prevailing at the balance sheet date with the results of operations of subsidiaries translated at the weighted average exchange rate for the reporting period. The cumulative foreign currency translation adjustment is recorded as a component of accumulated other comprehensive income (loss) in shareholders' equity.

Transactions in foreign currencies are translated into the functional currency of the relevant subsidiary at the weighted average exchange rate for the reporting period. Any monetary assets and liabilities arising from these transactions are translated into the relevant functional currency at exchange rates prevailing at the balance sheet date or on settlement. Resulting gains and losses are recorded in foreign exchange gain (loss) in our consolidated statements of income (loss).

Deferred Financing Costs

Deferred financing costs are reported at cost, less accumulated amortization and are presented in the consolidated balance sheets as a direct deduction from the carrying value of the associated debt, with the exception of deferred financing costs associated with revolving-debt arrangements which are presented as assets. The related amortization expense is included in interest expense, net in our consolidated statements of income (loss).

Contingencies

From time to time, we may become involved in claims and other legal matters arising in the ordinary course of business. We record accruals for loss contingencies to the extent that we conclude that it is probable that a liability has been incurred and the amount of the related loss can be reasonably estimated. Legal fees and other expenses related to litigation are expensed as incurred and included in selling, general and administrative expenses.

Share-Based Compensation

We account for compensation cost for all share-based awards at fair value on the date of grant. The fair value is recognized as expense over the service period, net of estimated forfeitures, using the straight-line method. The estimation of share-based awards that will ultimately vest requires judgment, and, to the extent actual results or updated estimates differ from current estimates, such amounts will be recorded as a cumulative adjustment in the period estimates are revised. We primarily consider historical experience when estimating expected forfeitures.

Performance-Based Restricted Stock Unit Awards

Performance-based restricted stock units, or PRSUs, awarded to employees vest upon the achievement of certain performance criteria at the end of a specified performance period, subject to a relative total shareholder return, or TSR, modifier. The estimated fair value of these PRSUs is based on a Monte Carlo simulation model. Compensation expense for PRSUs is recognized from the date the Company determines the performance criteria probable of being achieved to the date the award, or relevant portion of the award, is expected to vest. Cumulative adjustments are recorded on a quarterly basis to reflect subsequent changes to the estimated outcome of the performance criteria until the date results are determined.

Variable Interest Entity

In the year ended December 31, 2021, we invested in a cell of a protected cell company, or the protected cell, as part of our directors' and officers' liability risk financing strategy. Based on our control and the structure of the protected cell, we concluded that Jazz is the primary beneficiary of the protected cell and is required to consolidate the protected cell. The insurance premium payable to the protected cell for the year ended December 31, 2021 and the protected cell's assets and liabilities as of December 31, 2021 were immaterial.

Recent Accounting Pronouncements

In August 2020, the FASB issued ASU No. 2020-06, "Debt—Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging— Contracts in Entity's Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity's Own Equity", which simplifies the accounting for convertible instruments by eliminating the requirement to separate embedded conversion features from the host contract when the conversion features are not required to be accounted for as derivatives under Topic 815, Derivatives and Hedging, or that do not result in substantial premiums accounted for as paid-in capital. By removing the separation model, a convertible debt instrument will be reported as a single liability instrument with no separate accounting for embedded conversion features. This new standard also removes certain settlement conditions that are required for contracts to qualify for equity classification and eliminates the treasury stock method to calculate diluted earnings per share for convertible instruments and requires the use of the if-converted method. The Company adopted ASU 2020-06 on January 1, 2022, on a modified retrospective basis. As a result of adoption, the Company

increased its convertible debt liabilities, retained earnings and deferred tax assets on January 1, 2022 by $206.2 million, $127.4 million and $0.1 million, respectively and decreased its additional paid-in capital by $333.5 million.

In October 2021, the FASB issued ASU 2021-08, “Business Combinations (Topic 805): Accounting for Contract Assets and Contract Liabilities from Contracts with Customers”, which requires entities to recognize and measure contract assets and contract liabilities acquired in a business combination in accordance with ASC 2014-09, “Revenue from Contracts with Customers (Topic 606)”. The update will generally result in an entity recognizing contract assets and contract liabilities at amounts consistent with those recorded by the acquiree immediately before the acquisition date rather than at fair value. The new standard is effective on a prospective basis for fiscal years beginning after December 15, 2022, with early adoption permitted. The new guidance is not expected to have a material impact on our results of operations, financial position, or cash flows.

3. Business Combination, Asset Acquisitions and Collaborations

GW Acquisition

On May 5, 2021, or the Closing Date, we acquired the entire issued share capital of GW. As a result, GW became an indirect wholly owned subsidiary of the Company.

We acquired GW with the objective of broadening our neuroscience portfolio, further diversifying our revenue and driving sustainable, long-term value creation opportunities. GW was a global leader in discovering, developing, manufacturing and commercializing novel, regulatory approved therapeutics from its proprietary cannabinoid research platform to address a broad range of diseases.

The aggregate consideration for the GW Acquisition was $7.2 billion as follows (all amounts in thousands except American Depositary Shares, or ADS, and per GW ADS amounts):

GW ADS outstanding May 5, 2021		31,556,200
Cash consideration per GW ADS	$	200
Total cash consideration to GW ADS holders	$	6,311,240
Cash consideration to GW share option holders (inclusive of payroll taxes)		267,450
Total cash consideration		6,578,690
Equity consideration to GW ADS holders (1)		608,456
Consideration related to replacement share option pre-combination service		3,555
Total equity consideration		612,011
Total purchase consideration	$	7,190,701

(1) 3.8 million ordinary shares were issued to GW ADS holders. The closing price of the ordinary shares on May 4, 2021 ($160.20) was used to determine the fair value of this equity consideration because the closing of the transaction on May 5, 2021 occurred prior to the opening of regular trading.

In April 2021, we closed an offering of $1.5 billion in aggregate principal amount of 4.375% senior secured notes, due 2029, or the Secured Notes. In May 2021, we entered into a credit agreement, or the Credit Agreement, that provides for (i) a seven-year $3.1 billion term loan B facility, or the Dollar Term Loan, (ii) a seven-year €625.0 million term loan B facility, or the Euro Term Loan and, together with the Dollar Term Loan, collectively known as the Term Loan and (iii) a five-year $500.0 million revolving credit facility, or the Revolving Credit Facility. We financed the cash portion of the GW Acquisition consideration through a combination of cash on hand and borrowings under the Term Loan and the Secured Notes. For further information on the Term Loan and the Secured Notes, please see Note 12.

The GW Acquisition was accounted for as a business combination using the acquisition method under which assets and liabilities of GW were recorded at their respective estimated fair values as of the Closing Date and added to the assets and liabilities of the Company, including an amount for goodwill representing the difference between the acquisition consideration and the estimated fair value of the identifiable net assets. The results of operations of GW and the estimated fair values of the assets acquired and liabilities assumed have been included in our consolidated financial statements since the Closing Date.

In 2021, we incurred $81.9 million in acquisition-related costs related to the GW Acquisition, which primarily consisted of banking, legal, accounting and valuation-related expenses. These expenses were recorded in selling, general and administrative expense in the accompanying consolidated statements of income (loss). In 2021, our consolidated statements of

income (loss) included revenues of $476.4 million and a net loss of $704.6 million from the acquired GW business, as measured from the Closing Date.

The following table summarizes the preliminary fair values of assets acquired and liabilities assumed at the Closing Date before and after the measurement period adjustment (in thousands):

	Before Measurement Period Adjustment	Measurement Period Adjustment	After Measurement Period Adjustment
Cash and cash equivalents	$ 343,898	$ —	$ 343,898
Accounts receivable	76,355	—	76,355
Inventory	1,206,290	—	1,206,290
Prepaid expenses and other current assets	72,758	—	72,758
Property, plant and equipment	154,407	—	154,407
Acquired developed technologies	5,480,000	—	5,480,000
In-process research and development	160,000	—	160,000
Total acquired identifiable intangible assets	5,640,000	—	5,640,000
Goodwill	947,831	(14,597)	933,234
Deferred tax liabilities, net	(1,083,673)	14,597	(1,069,076)
Accrued liabilities	(131,971)	—	(131,971)
Other assets/liabilities	(35,194)	—	(35,194)
Total purchase consideration	$ 7,190,701	$ —	$ 7,190,701

The fair value estimates for the assets acquired and liabilities assumed were based upon preliminary calculations, and our estimates and assumptions are subject to change as we obtain additional information for our estimates during the measurement period (up to one year from the Closing Date). During the three months ended December 31, 2021, we recorded a measurement period adjustment which reduced deferred tax liabilities, net and goodwill by $14.6 million. The measurement period adjustment primarily related to the refinement of the opening UK net operating loss position of GW.

Inventory

Inventories acquired included raw materials, work in progress and finished goods. Inventories were recorded at their estimated fair values. The inventory was valued at estimated selling price less the estimated costs to be incurred to complete (in the case of work in progress) and sell the inventory, the associated margins on these activities and holding costs. A step-up in value of inventory of $1,062.6 million was recorded in connection with the GW Acquisition. The step-up expense will be recorded in cost of product sales on our consolidated statements of income (loss) as the inventory is sold to customers from the Closing Date.

Intangible assets

The fair value of acquired intangible assets was $5,640.0 million. The intangible assets include acquired developed technologies, primarily related to Epidiolex, and IPR&D.

The fair value of the Epidiolex acquired developed technology asset was determined by applying the income approach, which recognizes that the fair value of an asset is premised upon the expected receipt of future economic benefits such as earnings and cash inflows based on current sales projections and estimated direct costs, using a discount rate of 9.4% that reflects the return requirements of the market. This intangible asset is being amortized over an estimated useful life of 12 years.

Acquired IPR&D relates to nabiximols, which is currently in Phase 3 clinical trials for the treatment of spasticity associated with multiple sclerosis and spinal cord injury. The fair value of acquired IPR&D was determined using the income approach, including the application of probability factors related to the likelihood of success of nabiximols reaching final development and commercialization. The fair value of acquired IPR&D was capitalized as of the Closing Date and is subsequently accounted for as an indefinite-lived intangible asset until completion or abandonment of the associated research and development efforts. Accordingly, during the development period after the Closing Date, this asset will not be amortized into earnings; instead, it will be subject to periodic impairment testing.

Some of the more significant assumptions inherent in the development of intangible asset fair values include: the amount and timing of projected future cash flows (including revenue, cost of sales, research and development cost and sales and

marketing expenses); probability of success; the discount rate selected to measure inherent risk of future cash flows; and the assessment of the asset's life cycle and the competitive trends impacting the asset, among other factors.

Deferred tax liabilities, net

The net deferred tax liability relates to the difference between the financial statement carrying amount and the tax basis of acquired intangible assets and inventory, partially offset by acquired net operating loss carryforwards and other temporary differences.

Other tangible assets and liabilities

Other tangible assets and liabilities were valued at their respective carrying amounts as management believes that these amounts approximated their acquisition-date fair values.

Goodwill

Goodwill represents the excess of the total purchase consideration over the estimated fair value of net assets acquired and was recorded in the consolidated balance sheet as of the Closing Date. The goodwill was primarily attributable to the establishment of the deferred tax liability for the acquired intangible assets and inventory. We do not expect any portion of this goodwill to be deductible for income tax purposes.

Pro Forma Financial Information (Unaudited)

The following unaudited supplemental pro forma information presents the combined historical results of income (loss) of the Company and GW for 2021 and 2020, respectively, as if the GW Acquisition had been completed on January 1, 2020. The primary pro forma adjustments include:

- The exclusion of acquisition-related and integration expenses of $357.6 million in 2021 and related income tax expense of $23.6 million. The inclusion of acquisition-related and integration expenses of $386.7 million in 2020 and related income tax benefit of $27.9 million.
- An increase in amortization expense of $159.1 million in 2021 and related income tax benefit of $30.2 million. An increase in amortization expense of $464.6 million in 2020 and related income tax benefit of $88.3 million.
- An increase in cost of product sales of $81.9 million in 2021 and related income tax benefit of $12.4 million. An increase in cost of product sales of $296.3 million in 2020 and related income tax benefit of $59.5 million.
- An increase in interest expense of $49.1 million in 2021 and related income tax benefit of $9.0 million. An increase in interest expense of $241.0 million in 2020 and related income tax benefit of $51.9 million. The increase in interest arose on additional borrowings made to partially fund the GW Acquisition as if the borrowings had occurred on January 1, 2020.

The unaudited pro forma results do not assume any operating efficiencies as a result of the consolidation of operations and are as follows (in thousands):

	Year Ended December 31,	
	2021	2020
Total revenues	$ 3,294,697	$ 2,890,772
Net loss	$ (422,588)	$ (980,481)

Asset Acquisition and Exclusive License Agreement

In October 2020, we entered into an asset purchase and exclusive license agreement with SpringWorks Therapeutics, Inc., or SpringWorks, under which we acquired SpringWorks' fatty acid amide hydrolase, or FAAH, inhibitor program. Under the terms of the agreement, SpringWorks has assigned or exclusively licensed all assets relating to its FAAH inhibitor program to us, including assignment of SpringWorks' proprietary FAAH inhibitor PF-04457845, or PF-'845, now named JZP150 and its license agreement with Pfizer, Inc., or Pfizer, under which Pfizer exclusively licensed PF-'845 to SpringWorks in 2017. In addition to assuming all milestone and royalty obligations owed by SpringWorks to Pfizer, we made an upfront payment of $35.0 million to SpringWorks, which was recorded as acquired IPR&D expense in our consolidated statement of income for the year ended December 31, 2020, and may make potential milestone payments to SpringWorks of up to $375.0 million upon the achievement of certain clinical, regulatory and commercial milestones, and pay incremental tiered royalties to SpringWorks on future net sales of JZP150 in the mid- to high-single digit percentages.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS—(Continued)

License Agreement

In December 2019, we entered into an exclusive license agreement, or original license agreement, with Pharma Mar, S.A., or PharmaMar, for development and U.S. commercialization of Zepzelca. Zepzelca was granted orphan drug designation for relapsed SCLC by FDA in August 2018. In December 2019, PharmaMar submitted a new drug application, or NDA, to FDA for accelerated approval of Zepzelca for relapsed SCLC based on data from a Phase 2 trial, and in February 2020, FDA accepted the NDA for filing with priority review. In June 2020, FDA approved the NDA for Zepzelca for the treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy.

Under the terms of the original license agreement, which became effective in January 2020 upon expiration of the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, we paid PharmaMar an upfront payment of $200.0 million, which was recorded as acquired IPR&D expense in our consolidated statement of income for the year ended December 31, 2020. In June 2020, we made a milestone payment of $100.0 million to PharmaMar following FDA accelerated approval of Zepzelca, which was capitalized as an intangible asset on our consolidated balance sheet. In October 2021, we reached our first sales milestone triggering a payment of $25.0 million, which was capitalized as an intangible asset on our consolidated balance sheet.

PharmaMar is eligible to receive potential future regulatory milestone payments of up to $150.0 million upon the achievement of continued U.S. regulatory approval of Zepzelca following the successful completion of confirmatory trials within certain timelines. PharmaMar is also eligible to receive up to $525.0 million in potential U.S. commercial milestone payments, as well as incremental tiered royalties on future net sales of Zepzelca ranging from the high teens up to 30 percent. PharmaMar may receive additional payments on approval of other indications, with any such payments creditable against commercial milestone payment obligations. PharmaMar retains production rights for Zepzelca and will supply the product to us.

In October 2020, we entered into an amendment and restatement of the original license agreement with PharmaMar, or the amended license agreement, which expanded our exclusive license to include rights to develop and commercialize Zepzelca in Canada. To date, we have paid PharmaMar an upfront payment of $1.0 million, which was recorded as acquired IPR&D expense in our consolidated statement of income for the year ended December 31, 2020, and a milestone payment of $1.0 million in September 2021 following the first NDA Approval by Health Canada, which was capitalized as an intangible asset on our consolidated balance sheet. PharmaMar is also eligible to receive up to $6.0 million in potential Canadian regulatory and commercial milestone payments, as well as incremental tiered royalties on future Canadian net sales of Zepzelca ranging from the high teens up to 30 percent.

Asset Acquisition

In August 2019, we announced the acquisition of Cavion, Inc., or Cavion, a clinical-stage biotechnology company, for an upfront payment of $52.5 million with the potential for additional payments of up to $260.0 million upon the achievement of certain clinical, regulatory and commercial milestones, for a total potential consideration of $312.5 million. As a result of the acquisition, we added JZP385, a modulator of T-type calcium channels, for the potential treatment of essential tremor, to our clinical pipeline. The acquisition of Cavion was accounted for as an asset acquisition because it did not meet the definition of a business.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS—(Continued)

The following table summarizes the total consideration for the acquisition and the value of assets acquired and liabilities assumed (in thousands):

Consideration		
Upfront payment for acquisition of Cavion's outstanding shares	$	52,500
Cash acquired		397
Working capital adjustment		(255)
Transaction costs		2,829
Total consideration	$	55,471
Assets Acquired and Liabilities Assumed		
Cash	$	397
In-process research and development		48,275
Deferred tax assets		7,995
Other assets and liabilities		(1,196)
Total net assets acquired	$	55,471

The value attributed to in-process research and development related to JZP385 and was expensed as it was determined to have no alternative future use.

Collaboration and License Agreement

In January 2019, we entered into a strategic collaboration agreement with Codiak BioSciences, Inc., or Codiak, focused on the research, development and commercialization of exosome therapeutics to treat cancer. Codiak granted us an exclusive, worldwide, royalty-bearing license to develop, manufacture and commercialize therapeutic candidates directed at five targets to be developed using Codiak's engEx™ precision engineering platform for exosome therapeutics.

Under the terms of the agreement, Codiak is responsible for the execution of preclinical and early clinical development of therapeutic candidates directed at all five targets through Phase 1/2 proof of concept studies. Following the conclusion of the applicable Phase 1/2 study, we will be responsible for future development, potential regulatory submissions and commercialization for each product. Codiak has the option to participate in co-commercialization and cost/profit-sharing in the U.S. and Canada on up to two products.

As part of the agreement, we paid Codiak an upfront payment of $56.0 million in January 2019, which was recorded as acquired IPR&D expense in our consolidated statement of income for the year ended December 31, 2020. Codiak is eligible to receive up to $20.0 million in preclinical development milestone payments. Codiak is also eligible to receive milestone payments totaling up to $200.0 million per target based on investigational new drug application acceptance, clinical and regulatory milestones, including approvals in the U.S., the European Union and Japan, and certain sales milestones. Codiak is also eligible to receive tiered royalties on net sales of each approved product.

Collaboration and Option Agreement

In 2017, we entered into a collaboration and option agreement with ImmunoGen, Inc. and we paid them a non-refundable upfront payment of $75.0 million, which was charged to acquired IPR&D expense upon closing of the transaction.

This agreement was amended in November 2019. Under the amended agreement we had the right to opt into an exclusive, worldwide license to develop and commercialize IMGN632, a CD123-targeted antibody-drug conjugate for hematological malignancies. In December 2020, we exercised our opt-out rights with respect to IMGN632, thereby relinquishing the development and commercialization option.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS—(Continued)

4. Cash and Available-for-Sale Securities

Cash and cash equivalents and investments consisted of the following (in thousands):

	December 31, 2021					
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value	Cash and Cash Equivalents	Investments
Cash	$ 510,747	$ —	$ —	$ 510,747	$ 510,747	$ —
Money market funds	80,701	—	—	80,701	80,701	—
Totals	$ 591,448	$ —	$ —	$ 591,448	$ 591,448	$ —

	December 31, 2020					
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value	Cash and Cash Equivalents	Investments
Cash	$ 517,117	$ —	$ —	$ 517,117	$ 517,117	$ —
Time deposits	1,360,000	—	—	1,360,000	285,000	1,075,000
Money market funds	255,652	—	—	255,652	255,652	—
Totals	$ 2,132,769	$ —	$ —	$ 2,132,769	$ 1,057,769	$ 1,075,000

Cash equivalents and investments are considered available-for-sale securities. We use the specific-identification method for calculating realized gains and losses on securities sold and include them in interest expense, net in the consolidated statements of income (loss). Our investment balances represent time deposits with original maturities of greater than three months and less than one year. Interest income from available-for-sale securities was $1.8 million, $11.1 million and $20.5 million in 2021, 2020 and 2019, respectively.

5. Fair Value Measurement

The following table summarizes, by major security type, our available-for-sale securities and derivative contracts that were measured at fair value on a recurring basis and were categorized using the fair value hierarchy (in thousands):

	December 31, 2021			December 31, 2020		
	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Total Estimated Fair Value	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Total Estimated Fair Value
Assets:						
Available-for-sale securities:						
Time deposits	$ —	$ —	$ —	$ —	$ 1,360,000	$ 1,360,000
Money market funds	80,701	—	80,701	255,652	—	255,652
Foreign exchange forward contracts	—	580	580	—	11,907	11,907
Totals	$ 80,701	$ 580	$ 81,281	$ 255,652	$ 1,371,907	$ 1,627,559
Liabilities:						
Cross-currency interest rate contracts	$ —	$ 15,232	$ 15,232	$ —	$ —	$ —
Interest rate contracts	—	—	—	—	2,835	2,835
Foreign exchange forward contracts	—	3,187	3,187	—	790	790
Totals	$ —	$ 18,419	$ 18,419	$ —	$ 3,625	$ 3,625

As of December 31, 2021 our available-for-sale securities were comprised of money market funds and the carrying value was approximately equal to the fair values. Money market funds were measured using quoted prices in active markets, which represent Level 1 inputs. As of December 31, 2020 our available-for-sale securities comprised money market funds and time deposits. Time deposits were measured at fair value using Level 2 inputs. Level 2 inputs are obtained from various third party data providers and represent quoted prices for similar assets in active markets, or these inputs were derived from observable market data, or if not directly observable, were derived from or corroborated by other observable market data.

Our derivative assets and liabilities include cross-currency interest rate and foreign exchange derivatives that are measured at fair value using observable market inputs such as forward rates, interest rates, our own credit risk as well as an evaluation of our counterparties' credit risks. Based on these inputs, the derivative assets and liabilities are classified within Level 2 of the fair value hierarchy. The interest rate swap agreements matured in July 2021.

There were no transfers between the different levels of the fair value hierarchy in 2021 or in 2020.

As of December 31, 2021 and 2020, the carrying amount of investments measured using the measurement alternative for equity investments without a readily determinable fair value was $5.0 million and $4.5 million, respectively. The carrying amount, which is recorded within other non-current assets, is based on the latest observable transaction price.

As of December 31, 2021, the estimated fair values of our 1.50% exchangeable senior notes due 2024, or the 2024 Notes, and our 2.00% exchangeable senior notes due 2026, or the 2026 Notes, were approximately $576.0 million and $1.1 billion, respectively. The 2024 Notes and the 2026 Notes, together with the 1.875% exchangeable senior notes due 2021, or the 2021 Notes, that were repurchased on maturity on August 15, 2021, are collectively known as the Exchangeable Senior Notes. As of December 31, 2021, the estimated fair value of the Secured Notes, the Dollar Term Loan and the Euro Term Loan, were approximately $1.6 billion, $3.1 billion and $236.0 million, respectively. The fair values of each of these debt facilities was estimated using quoted market prices obtained from brokers (Level 2).

6. Derivative Instruments and Hedging Activities

We are exposed to certain risks arising from operating internationally, including fluctuations in foreign exchange rates primarily related to the translation of the Euro Term Loan and sterling and euro-denominated net monetary liabilities, including intercompany balances, held by subsidiaries with a U.S. dollar functional currency. We manage these exposures within specified guidelines through the use of derivatives. All of our derivative instruments are utilized for risk management purposes, we do not use derivatives for speculative trading purposes.

In order to hedge our exposure to foreign currency exchange risk associated with our Euro Term Loan, we entered into a cross-currency interest rate swap contract in May 2021 with a maturity date of March 31, 2022. The terms of this contract convert the principal repayments and interest payments on our Euro Term Loan into U.S. dollar. As of December 31, 2021, the cross-currency interest rate swap had a notional amount of $251.0 million which is designated for accounting purposes as a fair value hedge. The carrying amount of the Euro Term Loan and the fair value of the cross-currency interest rate swap contract will be remeasured with changes in the euro to U.S. dollar foreign exchange rates recognized within foreign exchange loss in the consolidated statements of income (loss).

The impact on accumulated other comprehensive income (loss) and earnings from the cross-currency interest rate swap contract was as follows (in thousands):

Cross-Currency Interest Rate Contract:	Year Ended December 31, 2021
Loss recognized in accumulated other comprehensive income (loss), net of tax	$ (375)
Loss reclassified from accumulated other comprehensive income (loss) to foreign exchange loss, net of tax	246
Loss recognized in foreign exchange loss	35,885

During the next 12 months, we expect to reclassify $0.1 million of losses, net of tax, on the cross-currency interest rate contract recognized in accumulated other comprehensive income (loss) to foreign exchange gain (loss).

We enter into foreign exchange forward contracts, with durations of up to 12 months, designed to limit the exposure to fluctuations in foreign exchange rates related to the translation of certain non-U.S. dollar denominated liabilities, including intercompany balances. Hedge accounting is not applied to these derivative instruments as gains and losses on these hedge transactions are designed to offset gains and losses on underlying balance sheet exposures. As of December 31, 2021 and 2020, the notional amount of foreign exchange contracts where hedge accounting was not applied was $347.2 million and $357.4 million, respectively.

The foreign exchange loss in our consolidated statements of income (loss) included the following gains and losses associated with foreign exchange contracts not designated as hedging instruments (in thousands):

	Year Ended December 31,		
Foreign Exchange Forward Contracts:	2021	2020	2019
Gain (loss) recognized in foreign exchange loss	$ (19,585)	$ 19,843	$ (6,192)

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS—(Continued)

The cash flow effects of our derivative contracts are included within net cash provided by operating activities in the consolidated statements of cash flows, except for the settlement of notional amounts of the cross-currency swap, which are included in net cash provided by (used in) financing activities.

To achieve a desired mix of floating and fixed interest rates on our variable rate debt, we entered into interest rate swap agreements in March 2017. In May 2021, we repaid the term loan to which these interest rate swap agreements related, at which point the interest rate swap contracts were de-designated as cash flow hedges. The interest rate swap agreements matured in July 2021.

The impact on accumulated other comprehensive income (loss) and earnings from interest rate swap contracts was as follows (in thousands):

	Year Ended December 31,		
Interest Rate Contracts:	**2021**	**2020**	**2019**
Loss recognized in accumulated other comprehensive income (loss), net of tax	$ (14)	$ (4,543)	$ (3,903)
Loss (gain) reclassified from accumulated other comprehensive income (loss) to interest expense, net of tax	$ 2,482	$ 3,401	$ (979)

The following tables summarize the fair value of outstanding derivatives (in thousands):

	December 31, 2021			
	Asset Derivatives		Liability Derivatives	
	Balance Sheet Location	**Fair Value**	**Balance Sheet Location**	**Fair Value**
Derivatives designated as hedging instruments:				
Cross-currency interest rate contracts	Other current assets	$ —	Accrued liabilities	$ 15,232
Derivatives not designated as hedging instruments:				
Foreign exchange forward contracts	Other current assets	580	Accrued liabilities	3,187
Total fair value of derivative instruments		$ 580		$ 18,419

	December 31, 2020			
	Asset Derivatives		Liability Derivatives	
	Balance Sheet Location	**Fair Value**	**Balance Sheet Location**	**Fair Value**
Derivatives designated as hedging instruments:				
Interest rate contracts	Other current assets	$ —	Accrued liabilities	$ 2,835
Derivatives not designated as hedging instruments:				
Foreign exchange forward contracts	Other current assets	11,907	Accrued liabilities	790
Total fair value of derivative instruments		$ 11,907		$ 3,625

Although we do not offset derivative assets and liabilities within our consolidated balance sheets, our International Swap and Derivatives Association agreements provide for net settlement of transactions that are due to or from the same counterparty upon early termination of the agreement due to an event of default or other termination event. The following tables summarize the potential effect on our consolidated balance sheets of offsetting our interest rate contracts and foreign exchange forward contracts subject to such provisions (in thousands):

	December 31, 2021					
				Gross Amounts Not Offset in the Consolidated Balance Sheet		
Description	**Gross Amounts of Recognized Assets/ Liabilities**	**Gross Amounts Offset in the Consolidated Balance Sheet**	**Net Amounts of Assets/ Liabilities Presented in the Consolidated Balance Sheet**	**Derivative Financial Instruments**	**Cash Collateral Received (Pledged)**	**Net Amount**
Derivative assets	$ 580	$ —	$ 580	$ (567)	$ —	$ 13
Derivative liabilities	$ (18,419)	$ —	$ (18,419)	$ 567	$ —	$ (17,852)

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS—(Continued)

	December 31, 2020					
				Gross Amounts Not Offset in the Consolidated Balance Sheet		
Description	Gross Amounts of Recognized Assets/ Liabilities	Gross Amounts Offset in the Consolidated Balance Sheet	Net Amounts of Assets/ Liabilities Presented in the Consolidated Balance Sheet	Derivative Financial Instruments	Cash Collateral Received (Pledged)	Net Amount
Derivative assets	$ 11,907	$ —	$ 11,907	$ (2,207)	$ —	$ 9,700
Derivative liabilities	$ (3,625)	$ —	$ (3,625)	$ 2,207	$ —	$ (1,418)

7. Inventories

Inventories consisted of the following (in thousands):

	December 31,	
	2021	2020
Raw materials	$ 21,550	$ 16,003
Work in process	886,849	45,758
Finished goods	164,322	33,635
Total inventories	$ 1,072,721	$ 95,396

As of December 31, 2021, inventories included $811.3 million related to the purchase accounting inventory fair value step-up on inventory acquired in the GW Acquisition.

8. Other Current Assets

Other current assets consisted of the following (in thousands):

	December 31,	
	2021	2020
Deferred charge for income taxes on intercompany profit	$ 203,480	$ 114,234
Other	48,912	38,257
Total other current assets	$ 252,392	$ 152,491

9. Property, Plant and Equipment

Property, plant and equipment consisted of the following (in thousands):

	December 31,	
	2021	2020
Construction-in-progress	$ 86,511	$ 7,262
Manufacturing equipment and machinery	69,079	33,465
Leasehold improvements	66,318	54,113
Land and buildings	64,008	47,555
Computer software	25,646	22,781
Computer equipment	16,234	18,749
Furniture and fixtures	14,412	11,598
Subtotal	342,208	195,523
Less accumulated depreciation and amortization	(85,371)	(67,588)
Property, plant and equipment, net	$ 256,837	$ 127,935

Depreciation and amortization expense on property, plant and equipment amounted to $26.7 million, $18.7 million and $15.3 million for the years ended December 31, 2021, 2020 and 2019, respectively.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS—(Continued)

10. Goodwill and Intangible Assets

The gross carrying amount of goodwill was as follows (in thousands):

Balance at December 31, 2020	$ 958,303
Goodwill arising from the GW Acquisition	933,234
Foreign exchange	(63,928)
Balance at December 31, 2021	$ 1,827,609

The gross carrying amounts and net book values of our intangible assets were as follows (in thousands):

		December 31, 2021			December 31, 2020		
	Remaining Weighted-Average Useful Life (In years)	Gross Carrying Amount	Accumulated Amortization	Net Book Value	Gross Carrying Amount	Accumulated Amortization	Net Book Value
Acquired developed technologies	11.4	$ 8,195,675	$ (1,198,333)	$ 6,997,342	$ 3,379,162	$ (1,184,111)	$ 2,195,051
Manufacturing contracts	—	12,124	(12,124)	—	13,135	(13,135)	—
Trademarks	—	2,893	(2,893)	—	2,917	(2,917)	—
Total finite-lived intangible assets		8,210,692	(1,213,350)	6,997,342	3,395,214	(1,200,163)	2,195,051
Acquired IPR&D assets		154,986	—	154,986	—	—	—
Total intangible assets		$ 8,365,678	$ (1,213,350)	$ 7,152,328	$ 3,395,214	$ (1,200,163)	$ 2,195,051

The increase in the gross carrying amount of intangible assets as of December 31, 2021 compared to December 31, 2020 primarily reflects the intangible assets arising from the GW Acquisition, as described in Note 3, partially offset by the de-recognition of the fully amortized Erwinaze intangible assets and the negative impact of foreign currency translation adjustments due to the weakening of sterling and euro against the U.S. dollar.

The assumptions and estimates used to determine future cash flows and remaining useful lives of our intangible and other long-lived assets are complex and subjective. They can be affected by various factors, including external factors, such as industry and economic trends, and internal factors such as changes in our business strategy and our forecasts for specific product lines.

Based on finite-lived intangible assets recorded as of December 31, 2021, and assuming the underlying assets will not be impaired and that we will not change the expected lives of any other assets, future amortization expenses were estimated as follows (in thousands):

Year Ending December 31,	Estimated Amortization Expense
2022	$ 627,866
2023	627,866
2024	627,866
2025	627,866
2026	627,866
Thereafter	3,858,012
Total	$ 6,997,342

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS—(Continued)

11. Accrued Liabilities

Accrued liabilities consisted of the following (in thousands):

	December 31,	
	2021	2020
Rebates and other sales deductions	$ 215,397	$ 127,534
Employee compensation and benefits	158,870	102,601
Accrued interest	48,640	5,722
Clinical trial accruals	25,612	9,108
Accrued milestones	25,000	—
Consulting and professional services	22,507	6,660
Selling and marketing accruals	21,566	6,742
Accrued royalties	20,345	15,230
Derivative instrument liabilities	18,419	3,625
Inventory-related accruals	16,166	9,809
Sales return reserve	15,814	18,368
Current portion of lease liabilities	15,763	14,457
Accrued construction-in-progress	2,894	1,119
Other	59,311	31,757
Total accrued liabilities	$ 666,304	$ 352,732

12. Debt

The following table summarizes the carrying amount of our indebtedness (in thousands):

	December 31,	
	2021	2020
2021 Notes	$ —	$ 218,812
Unamortized discount and debt issuance costs on 2021 Notes	—	(5,883)
2021 Notes, net	—	212,929
2024 Notes	575,000	575,000
Unamortized discount and debt issuance costs on 2024 Notes	(71,237)	(95,275)
2024 Notes, net	503,763	479,725
2026 Notes	1,000,000	1,000,000
Unamortized discount and debt issuance costs on 2026 Notes	(150,730)	(179,518)
2026 Notes, net	849,270	820,482
Secured Notes	1,473,810	—
Term Loan	3,223,100	581,702
Total debt	6,049,943	2,094,838
Less current portion	31,000	246,322
Total long-term debt	$ 6,018,943	$ 1,848,516

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS—(Continued)

Credit Agreement

On May 5, 2021, the Company, Jazz Financing Lux S.à.r.l., or Jazz Lux, and certain of our other subsidiaries, as borrowers, (collectively with the Company and Jazz Lux, the "Borrowers"), entered into the Credit Agreement, that provides for (i) the Dollar Term Loan which was drawn by Jazz Lux on the Closing Date in U.S. dollars (ii) the Euro Term Loan which was drawn by Jazz Lux on the Closing Date in Euros and (iii) the Revolving Credit Facility, which is available to be drawn by any Borrower in U.S. dollars.

We used the proceeds from the Term Loan (i) to repay in full $575.9 million under that certain credit agreement, dated as of June 18, 2015 (as amended) among the Company, and certain of our other subsidiaries as borrowers, the lenders party thereto and Bank of America, N.A., as administrative agent and collateral agent, or the Existing Credit Agreement, (ii) to fund, in part, the cash consideration payable in connection with the GW Acquisition and (iii) to pay related fees and expenses. Upon the repayment in full of loans under the Existing Credit Agreement, it was terminated and all guarantees and liens thereunder were released.

Loans under the Term Loan and Revolving Credit Facility bear interest at a rate equal to (A) in the case of the Dollar Term Loan and the Revolving Credit Facility, at the applicable Borrower's option, either (a) London Inter-Bank Offered Rate, or LIBOR or (b) the prime lending rate and (B) in the case of the Euro Term Loan, Euro Inter-Bank Offered Rate, or EURIBOR, in each case, plus an applicable margin. The applicable margin for the Term Loan is 3.50% (in the case of LIBOR or EURIBOR borrowings) and 2.50% (in the case of borrowings at the prime lending rate). The applicable margin for the Revolving Credit Facility ranges from 3.25% to 2.75% (in the case of LIBOR borrowings) and 2.25% to 1.75% (in the case of borrowings at the prime lending rate), depending on our first lien secured net leverage ratio level. The Dollar Term Loan is subject to a LIBOR floor of 0.50%, the Euro Term Loan and loans under the Revolving Credit Facility are not subject to a EURIBOR or LIBOR (as applicable) floor. The Revolving Credit Facility has a commitment fee payable on the undrawn amount ranging from 0.50% to 0.40% per annum based upon our first lien secured net leverage ratio.

As of December 31, 2021, the interest rate and effective interest rate on the Dollar Term Loan were 4.00% and 4.55%, respectively. The interest rate and effective interest rate on the Euro Term Loan were 4.43% and 4.93%, respectively. As of December 31, 2021, we had an undrawn Revolving Credit Facility totaling $500.0 million.

The Borrowers' obligations under the Credit Agreement and any hedging or cash management obligations entered into with any lender thereunder are guaranteed by the Company, the other borrowers, and each of the Company's other existing or subsequently acquired or organized direct and indirect subsidiaries (subject to certain exceptions), or the Guarantors. We refer to the Borrowers and the Guarantors collectively as the "Loan Parties."

The Loan Parties' obligations under the Credit Agreement are secured, subject to customary permitted liens and other exceptions, by a security interest in (a) all tangible and intangible assets of the Loan Parties, except for certain excluded assets, and (b) all of the equity interests of the subsidiaries of the Loan Parties held by the Loan Parties.

We may make voluntary prepayments at any time without payment of a premium or penalty, subject to certain exceptions, and are required to make certain mandatory prepayments of outstanding indebtedness under the Credit Agreement in certain circumstances.

Principal repayments of the Dollar Term Loan, which are due quarterly, began in September 2021 and are equal to 1.0% per annum of the original principal amount of $3.1 billion with any remaining balance payable on the maturity date. The Euro Term Loan does not have any mandatory principal repayments during its term, however in September and December 2021, we made voluntary prepayments totaling €416.7 million or $502.0 million.

The Credit Agreement contains customary representations and warranties and customary affirmative and negative covenants applicable to the Company and its restricted subsidiaries, including, among other things, restrictions on indebtedness, liens, investments, mergers, dispositions, prepayment of junior indebtedness and dividends and other distributions. The Credit Agreement contains financial covenants that require the Company and its restricted subsidiaries to (a) not exceed a maximum first lien secured net leverage ratio and (b) not fall below a minimum interest coverage ratio, provided that such covenants apply only to the Revolving Credit Facility and are applicable only if amounts are drawn (or non-cash collateralized letters of credit in excess of $50 million are outstanding) under the Revolving Credit Facility. The Credit Agreement also contains customary events of default relating to, among other things, failure to make payments, breach of covenants and breach of representations.

2029 Senior Secured Notes

On April 29, 2021, Jazz Securities Designated Activity Company, or Jazz Securities, a direct wholly owned subsidiary of the Company, closed the offering of the Secured Notes in a private placement. We used the proceeds from the Secured Notes to fund, in part, the cash consideration payable in connection with the GW Acquisition.

Interest on the Secured Notes is payable semi-annually in arrears on January 15 and July 15 of each year, beginning on January 15, 2022, at a rate of 4.375% per year. The Secured Notes mature on January 15, 2029.

The Secured Notes are jointly and severally guaranteed by the Company and each of its restricted subsidiaries, other than Jazz Securities, that is a borrower, or a guarantor, under the Credit Agreement. The Secured Notes and related guarantees are secured by a first priority lien (subject to permitted liens and certain other exceptions), equally and ratably with the Credit Agreement, on the collateral securing the Credit Agreement.

Except as described below, the Secured Notes may not be optionally redeemed before July 15, 2024. Thereafter, some or all of the Secured Notes, may be redeemed at any time and from time to time at a specified redemption prices, plus accrued and unpaid interest, if any, to, but excluding, to the redemption date. Jazz Securities may redeem all but not part of the Secured Notes at its option at any time in connection with certain tax-related events and may redeem some or all of the Secured Notes at any time and from time to time prior to July 15, 2024 at a price equal to 100% of the principal amount of the Secured Notes to be redeemed plus a “make whole” premium, plus accrued and unpaid interest, if any, to, but excluding, the redemption date. In addition, Jazz Securities may redeem up to 40% of the aggregate principal amount of the Secured Notes at any time and from time to time prior to July 15, 2024, with the net proceeds of certain equity offerings at a price of 104.375% of the principal amount of such Secured Notes, plus accrued and unpaid interest, if any, to, but excluding, the redemption date. In addition, during each of the three consecutive twelve-month periods commencing on the issue date of the Secured Notes, Jazz Securities may redeem up to 10% of the original aggregate initial principal amount of the Secured Notes at a redemption price of 103% of the principal amount of such Secured Notes, plus accrued and unpaid interest, if any, to, but excluding, the redemption date.

If Jazz undergoes a change of control, Jazz Securities will be required to make an offer to purchase all of the Secured Notes at a purchase price in cash equal to 101% of the principal amount thereof, plus accrued and unpaid interest, if any, to, but excluding, the date of repurchase, subject to certain exceptions.

The indenture governing the Secured Notes contains customary affirmative covenants and negative covenants applicable to the Company and its restricted subsidiaries, including, among other things, restrictions on indebtedness, liens, investments, mergers, dispositions, prepayment of junior indebtedness and dividends and other distributions. If Jazz Securities or the Company’s restricted subsidiaries engage in certain asset sales, Jazz Securities will be required under certain circumstances to make an offer to purchase the Secured Notes at 100% of the principal amount, plus accrued and unpaid interest, if any, to, but excluding, the repurchase date.

As of December 31, 2021, the interest rate and effective interest rate on the Secured Notes were 4.375% and 4.64%, respectively.

Exchangeable Senior Notes Due 2026

In 2020 we completed a private placement of $1.0 billion principal amount of the 2026 Notes. We used a portion of the net proceeds from this offering to repurchase for cash $332.9 million aggregate principal amount of the 2021 Notes through privately-negotiated transactions concurrently with the offering of the 2026 Notes. Interest on the 2026 Notes is payable semi-annually in cash in arrears on June 15 and December 15 of each year, beginning on December 15, 2020, at a rate of 2.00% per year. In certain circumstances, we may be required to pay additional amounts as a result of any applicable tax withholding or deductions required in respect of payments on the 2026 Notes. The 2026 Notes mature on June 15, 2026, unless earlier exchanged, repurchased or redeemed.

The holders of the 2026 Notes have the ability to require us to repurchase all or a portion of their 2026 Notes for cash in the event we undergo certain fundamental changes, such as specified change of control transactions, our liquidation or dissolution or the delisting of our ordinary shares from any of The New York Stock Exchange, The Nasdaq Global Market, The Nasdaq Global Select Market or The Nasdaq Capital Market (or any of their respective successors). Additionally, the terms and covenants in the indenture related to the 2026 Notes include certain events of default after which the 2026 Notes may be due and payable immediately. Prior to June 15, 2026, we may redeem the 2026 Notes, in whole but not in part, subject to compliance with certain conditions, if we have, or on the next interest payment date would, become obligated to pay to the holder of any 2026 Notes additional amounts as a result of certain tax-related events. We also may redeem the 2026 Notes on or after June 20, 2023 and prior to March 15, 2026, in whole or in part, if the last reported sale price per ordinary share has been at least 130% of the exchange price then in effect for at least 20 trading days (whether or not consecutive) during any 30 consecutive trading day period ending on, and including, the trading day immediately preceding the date on which we provide the notice of redemption.

The 2026 Notes are exchangeable at an initial exchange rate of 6.4182 ordinary shares per $1,000 principal amount of 2026 Notes, which is equivalent to an initial exchange price of approximately $155.81 per ordinary share. Upon exchange, the 2026 Notes may be settled in cash, ordinary shares or a combination of cash and ordinary shares, at our election. Our intent and

policy is to settle the principal amount of the 2026 Notes in cash upon exchange. The exchange rate will be subject to adjustment in some events but will not be adjusted for any accrued and unpaid interest. In addition, following certain make-whole fundamental changes occurring prior to the maturity date of the 2026 Notes or upon our issuance of a notice of redemption, we will in certain circumstances increase the exchange rate for holders of the 2026 Notes who elect to exchange their 2026 Notes in connection with that make-whole fundamental change or during the related redemption period. Prior to March 15, 2026, the 2026 Notes will be exchangeable only upon satisfaction of certain conditions and during certain periods, and thereafter, at any time until the close of business on the second scheduled trading day immediately preceding the maturity date.

In accounting for the issuance of the 2026 Notes, we separated the 2026 Notes into liability and equity components. The carrying amount of the liability component was calculated by measuring the estimated fair value of a similar liability that does not have an associated exchange feature. The carrying amount of the equity component representing the exchange option was determined by deducting the fair value of the liability component from the face value of the 2026 Notes as a whole. The excess of the principal amount of the liability component over its carrying amount will be amortized to interest expense over the expected life of the 2026 Notes using the effective interest method with an effective interest rate of 5.98% per annum. We have determined the expected life of the 2026 Notes to be equal to the original 6-year term. The equity component is not remeasured as long as it continues to meet the conditions for equity classification. As of December 31, 2021, the “if converted value” of the 2026 Notes did not exceed the principal amount of the 2026 Notes. As of December 31, 2020, the “if converted value” of the 2026 Notes exceeded the principal amount by $59.3 million.

We allocated the total issuance costs incurred of $18.6 million to the liability and equity components based on their relative values. Issuance costs attributable to the liability component will be amortized to expense over the term of the 2026 Notes, and issuance costs attributable to the equity component were included with the equity component in our shareholders’ equity.

As of December 31, 2021 and 2020, the carrying value of the equity component of the 2026 Notes, net of equity issuance costs, was $176.3 million.

Exchangeable Senior Notes Due 2024

In 2017, we completed a private placement of $575.0 million principal amount of 2024 Notes. We used the net proceeds from this offering to repay $500.0 million in outstanding loans under the revolving credit facility and to pay related fees and expenses. We used the remainder of the net proceeds for general corporate purposes. Interest on the 2024 Notes is payable semi-annually in cash in arrears on February 15 and August 15 of each year, beginning on February 15, 2018, at a rate of 1.50% per year. In certain circumstances, we may be required to pay additional amounts as a result of any applicable tax withholding or deductions required in respect of payments on the 2024 Notes. The 2024 Notes mature on August 15, 2024, unless earlier exchanged, repurchased or redeemed.

The holders of the 2024 Notes have the ability to require us to repurchase all or a portion of their 2024 Notes for cash in the event we undergo certain fundamental changes, such as specified change of control transactions, our liquidation or dissolution or the delisting of our ordinary shares from The Nasdaq Global Select Market. Prior to August 15, 2024, we may redeem the 2024 Notes, in whole but not in part, subject to compliance with certain conditions, if we have, or on the next interest payment date would, become obligated to pay to the holder of any 2024 Notes additional amounts as a result of certain tax-related events. We also may redeem the 2024 Notes on or after August 20, 2021, in whole or in part, if the last reported sale price per ordinary share has been at least 130% of the exchange price then in effect for at least 20 trading days (whether or not consecutive) during any 30 consecutive trading day period ending on, and including, the trading day immediately preceding the date on which we provide the notice of redemption.

The 2024 Notes are exchangeable at an initial exchange rate of 4.5659 ordinary shares per $1,000 principal amount of 2024 Notes, which is equivalent to an initial exchange price of approximately $219.02 per ordinary share. Upon exchange, the 2024 Notes may be settled in cash, ordinary shares or a combination of cash and ordinary shares, at our election. Our intent and policy is to settle the principal amount of the 2024 Notes in cash upon exchange. The exchange rate will be subject to adjustment in some events but will not be adjusted for any accrued and unpaid interest. In addition, following certain make-whole fundamental changes occurring prior to the maturity date of the 2024 Notes or upon our issuance of a notice of redemption, we will in certain circumstances increase the exchange rate for holders of the 2024 Notes who elect to exchange their 2024 Notes in connection with that make-whole fundamental change or during the related redemption period. Prior to May 15, 2024, the 2024 Notes will be exchangeable only upon satisfaction of certain conditions and during certain periods, and thereafter, at any time until the close of business on the second scheduled trading day immediately preceding the maturity date.

In accounting for the issuance of the 2024 Notes, we separated the 2024 Notes into liability and equity components. The carrying amount of the liability component was calculated by measuring the estimated fair value of a similar liability that does

not have an associated exchange feature. The carrying amount of the equity component representing the exchange option was determined by deducting the fair value of the liability component from the face value of the 2024 Notes as a whole. The excess of the principal amount of the liability component over its carrying amount will be amortized to interest expense over the expected life of the 2024 Notes using the effective interest method with an effective interest rate of 6.8% per annum. We have determined the expected life of the 2024 Notes to be equal to the original seven-year term. The equity component is not remeasured as long as it continues to meet the conditions for equity classification. As of December 31, 2021 and 2020, the "if-converted value" did not exceed the principal amount of the 2024 Notes.

We allocated the total issuance costs incurred of $15.6 million to the liability and equity components based on their relative values. Issuance costs attributable to the liability component will be amortized to expense over the term of the 2024 Notes, and issuance costs attributable to the equity component were included with the equity component in our shareholders' equity.

As of December 31, 2021 and 2020, the carrying value of the equity component of the 2024 Notes, net of equity issuance costs, was $149.8 million.

Exchangeable Senior Notes Due 2021

In 2014, we completed a private placement of the 2021 Notes with a maturity date of August 15, 2021. Interest on the 2021 Notes was payable semi-annually in cash in arrears on February 15 and August 15 of each year, beginning on February 15, 2015, at a rate of 1.875% per year. The exchange rate was 5.0057 ordinary shares per $1,000 principal amount of 2021 Notes, which was equivalent to an exchange price of approximately $199.77 per ordinary share.

In accounting for the issuance of the 2021 Notes, we separated the 2021 Notes into liability and equity components. The carrying amount of the liability component was calculated by measuring the estimated fair value of a similar liability that does not have an associated exchange feature. The carrying amount of the equity component representing the exchange option was determined by deducting the fair value of the liability component from the face value of the 2021 Notes as a whole. The excess of the principal amount of the liability component over its carrying amount was amortized to interest expense over the expected life of the 2021 Notes using the effective interest method with an effective interest rate of 6.4% per annum.

We allocated the total issuance costs incurred of $16.1 million to the liability and equity components based on their relative values. Issuance costs attributable to the liability component were amortized to interest expense, net over the term of the 2021 Notes, and issuance costs attributable to the equity component were included with the equity component in our shareholders' equity. In 2020 we repurchased $356.2 million aggregate principal amount of the 2021 Notes and we repurchased the remaining $218.8 million aggregate principal amount on maturity in August 2021.

The Exchangeable Senior Notes were issued by Jazz Investments I Limited, or the Issuer, a 100%-owned finance subsidiary of Jazz Pharmaceuticals plc. The Exchangeable Senior Notes are senior unsecured obligations of the Issuer and are fully and unconditionally guaranteed on a senior unsecured basis by Jazz Pharmaceuticals plc. No subsidiary of Jazz Pharmaceuticals plc guaranteed the Exchangeable Senior Notes. Subject to certain local law restrictions on payment of dividends, among other things, and potential negative tax consequences, we are not aware of any significant restrictions on the ability of Jazz Pharmaceuticals plc to obtain funds from the Issuer or Jazz Pharmaceuticals plc's other subsidiaries by dividend or loan, or any legal or economic restrictions on the ability of the Issuer or Jazz Pharmaceuticals plc's other subsidiaries to transfer funds to Jazz Pharmaceuticals plc in the form of cash dividends, loans or advances. There is no assurance that in the future such restrictions will not be adopted.

For the years ended December 31, 2021, 2020 and 2019, we recognized $89.9 million, $87.6 million and $62.5 million, respectively, in interest expense, net related to the contractual coupon rate and the amortization of the debt discount and debt issuance costs on the Exchangeable Senior Notes.

Scheduled maturities with respect to our long-term debt are as follows (in thousands):

Year Ending December 31,	Scheduled Long-Term Debt Maturities
2022	$ 31,000
2023	31,000
2024	606,000
2025	31,000
2026	1,031,000
Thereafter	4,665,458
Total	$ 6,395,458

13. Leases

We have noncancelable leases for our buildings and growing facilities and we are obligated to make payments under noncancelable operating leases for automobiles used by our sales force.

The components of the lease expense for the years ended December 31, 2021, 2020 and 2019 were as follows (in thousands):

	Year Ended December 31,		
Lease Cost	**2021**	**2020**	**2019**
Operating lease cost	$ 23,869	$ 21,755	$ 23,087
Short-term lease cost	5,540	4,079	2,465
Variable lease cost	10	3	5
Sublease income	—	(224)	(634)
Finance Lease Cost			
Amortization of leased asset	324	—	—
Interest on lease liabilities	295	—	—
Net lease cost	$ 30,038	$ 25,613	$ 24,923

Supplemental balance sheet information related to operating and finance leases was as follows (in thousands):

		December 31,	
Leases	**Classification**	**2021**	**2020**
Assets			
Operating lease assets	Operating lease assets	$ 86,586	$ 129,169
Finance lease assets	Property, plant and equipment	5,738	—
Total lease assets		$ 92,324	$ 129,169
Liabilities			
Current			
Operating lease liabilities	Accrued liabilities	$ 15,357	$ 14,457
Finance lease liabilities	Accrued liabilities	406	—
Non-current			
Operating lease liabilities	Operating lease liabilities, less current portion	87,200	140,035
Finance lease liabilities	Other non-current liabilities	6,269	—
Total lease liabilities		$ 109,232	$ 154,492

	December 31,	
Lease Term and Discount Rate	**2021**	**2020**
Weighted-average remaining lease term (years)		
Operating leases	6.5	8.7
Finance leases	12.9	—
Weighted-average discount rate		
Operating leases	5.2 %	5.3 %
Finance leases	7.4 %	— %

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS—(Continued)

Supplemental cash flow information related to operating and finance leases was as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Cash paid for amounts included in the measurement of lease liabilities:			
Operating cash outflows from operating leases	$ 24,847	$ 21,678	$ 17,066
Operating cash outflows from finance leases	625	—	—
Financing cash outflows from finance leases	324	—	—
Non-cash operating activities:			
Operating lease assets obtained in exchange for new operating lease liabilities (1)	$ 8,188	$ 1,763	$ 153,448
Finance lease assets obtained in exchange for new finance lease liabilities	650	—	—
De-recognition of operating lease asset on lease assignment	56,968	—	—
De-recognition of operating lease liability on lease assignment	68,064	—	—

(1) Includes the balances recognized on January 1, 2019 on adoption of ASU No. 2016-02.

Maturities of operating and finance lease liabilities were as follows (in thousands):

Year Ending December 31,	Operating Leases	Finance Leases
2022	$ 20,373	$ 876
2023	19,426	872
2024	20,996	872
2025	14,565	872
2026	12,741	872
Thereafter	34,560	6,135
Total lease payments	$ 122,661	$ 10,499
Less imputed interest	(20,104)	(3,824)
Present value of lease liabilities	$ 102,557	$ 6,675

14. Commitments and Contingencies

Indemnification

In the normal course of business, we enter into agreements that contain a variety of representations and warranties and provide for general indemnification, including indemnification associated with product liability or infringement of intellectual property rights. Our exposure under these agreements is unknown because it involves future claims that may be made but have not yet been made against us. To date, we have not paid any claims or been required to defend any action related to these indemnification obligations.

We have agreed to indemnify our executive officers, directors and certain other employees for losses and costs incurred in connection with certain events or occurrences, including advancing money to cover certain costs, subject to certain limitations. The maximum potential amount of future payments we could be required to make under the indemnification obligations is unlimited; however, we maintain insurance policies that may limit our exposure and may enable us to recover a portion of any future amounts paid. Assuming the applicability of coverage, the willingness of the insurer to assume coverage, and subject to certain retention, loss limits and other policy provisions, we believe the fair value of these indemnification obligations is not significant. Accordingly, we did not recognize any liabilities relating to these obligations as of December 31, 2021 and December 31, 2020. No assurances can be given that the covering insurers will not attempt to dispute the validity, applicability, or amount of coverage without expensive litigation against these insurers, in which case we may incur substantial liabilities as a result of these indemnification obligations.

Other Commitments

As of December 31, 2021, we had $73.2 million of noncancelable purchase commitments due within one year, primarily related to agreements with third party manufacturers.

Legal Proceedings

We are involved in legal proceedings, including the following matters:

Xyrem Class Action

From June 2020 to October 2021, a number of lawsuits were filed on behalf of purported direct and indirect Xyrem purchasers, alleging that the patent litigation settlement agreements we entered with generic drug manufacturers who had filed Abbreviated New Drug Applications, or ANDA, violate state and federal antitrust and consumer protection laws, as follows:

On June 17, 2020, a class action lawsuit was filed in the United States District Court for the Northern District of Illinois by Blue Cross and Blue Shield Association, or BCBS, against Jazz Pharmaceuticals plc, Jazz Pharmaceuticals, Inc., and Jazz Pharmaceuticals Ireland Limited, or, collectively, the Company Defendants (hereinafter referred to as the BCBS Lawsuit). The BCBS Lawsuit also names Roxane Laboratories, Inc., Hikma Pharmaceuticals USA Inc., Eurohealth (USA), Inc., Hikma Pharmaceuticals plc, Amneal Pharmaceuticals LLC, Par Pharmaceuticals, Inc., Lupin Ltd., Lupin Pharmaceuticals Inc., and Lupin Inc., or, collectively, the BCBS Defendants.

On June 18 and June 23, 2020, respectively, two additional class action lawsuits were filed against the Company Defendants and the BCBS Defendants: one by the New York State Teamsters Council Health and Hospital Fund in the United States District Court for the Northern District of California, and another by the Government Employees Health Association Inc. in the United States District Court for the Northern District of Illinois (hereinafter referred to as the GEHA Lawsuit).

On June 18, 2020, a class action lawsuit was filed in the United States District Court for the Northern District of California by the City of Providence, Rhode Island, on behalf of itself and all others similarly situated, against Jazz Pharmaceuticals plc, and Roxane Laboratories, Inc., West-Ward Pharmaceuticals Corp., Hikma Labs Inc., Hikma Pharmaceuticals USA Inc., and Hikma Pharmaceuticals plc, or, collectively, the City of Providence Defendants.

On June 30, 2020, a class action lawsuit was filed in the United States District Court for the Northern District of Illinois by UFCW Local 1500 Welfare Fund on behalf of itself and all others similarly situated, against Jazz Pharmaceuticals Ireland Ltd., Jazz Pharmaceuticals, Inc., Roxane Laboratories, Inc., Hikma Pharmaceuticals plc, Eurohealth (USA), Inc. and West-Ward Pharmaceuticals Corp., or collectively the UFCW Defendants (hereinafter referred to as the UFCW Lawsuit).

On July 13, 2020, the plaintiffs in the BCBS Lawsuit and the GEHA Lawsuit dismissed their complaints in the United States District Court for the Northern District of Illinois and refiled their respective lawsuits in the United States District Court for the Northern District of California. On July 14, 2020, the plaintiffs in the UFCW Lawsuit dismissed their complaint in the United States District Court for the Northern District of Illinois and on July 15, 2020, refiled their lawsuit in the United States District Court for the Northern District of California.

On July 31, 2020, a class action lawsuit was filed in the United States District Court for the Southern District of New York by the A.F. of L.-A.G.C. Building Trades Welfare Plan on behalf of itself and all others similarly situated, against Jazz Pharmaceuticals plc (hereinafter referred to as the AFL Plan Lawsuit). The AFL Plan Lawsuit also names Roxane Laboratories Inc., West-Ward Pharmaceuticals Corp., Hikma Labs Inc., Hikma Pharmaceuticals plc, Amneal Pharmaceuticals LLC, Par Pharmaceuticals Inc., Lupin Ltd., Lupin Pharmaceuticals, Inc., and Lupin Inc.

On August 14, 2020, an additional class action lawsuit was filed in the United States District Court for the Southern District of New York by the Self-Insured Schools of California on behalf of itself and all others similarly situated, against the Company Defendants, as well as Hikma Pharmaceuticals plc, Eurohealth (USA) Inc., Hikma Pharmaceuticals USA, Inc., West-Ward Pharmaceuticals Corp., Roxane Laboratories, Inc., Amneal Pharmaceuticals LLC, Endo International, plc, Endo Pharmaceuticals LLC, Par Pharmaceutical, Inc., Lupin Ltd., Lupin Pharmaceuticals Inc., Lupin Inc., Sun Pharmaceutical Industries Ltd., Sun Pharmaceutical Holdings USA, Inc., Sun Pharmaceutical Industries, Inc., Ranbaxy Laboratories Ltd., Teva Pharmaceutical Industries Ltd., Watson Laboratories, Inc., Wockhardt Ltd., Morton Grove Pharmaceuticals, Inc., Wockhardt USA LLC, Mallinckrodt plc, and Mallinckrodt LLC (hereinafter referred to as the Self-Insured Schools Lawsuit).

On September 16, 2020, an additional class action lawsuit was filed in the United States District Court for the Northern District of California, by Ruth Hollman on behalf of herself and all others similarly situated, against the same defendants named in the Self-Insured Schools Lawsuit.

In December 2020, the above cases were centralized and transferred to the United States District Court for the Northern District of California, where the multidistrict litigation will proceed for the purpose of discovery and pre-trial proceedings.

On March 18, 2021, United Healthcare Services, Inc. filed a lawsuit in the United States District Court for the District of Minnesota against the Company Defendants, Hikma Pharmaceuticals plc, Roxane Laboratories, Inc., Hikma Pharmaceuticals USA Inc., Eurohealth (USA) Inc., Amneal Pharmaceuticals LLC, Par Pharmaceutical Inc., Lupin Ltd., and Lupin

Pharmaceuticals, Inc., raising similar allegations, or the UHS Lawsuit. On March 24, 2021, the U.S. Judicial Panel on Multidistrict Litigation conditionally transferred the UHS Lawsuit to the United States District Court for the Northern District of California, where it was consolidated for discovery and pre-trial proceedings with the other cases.

On August 13, 2021, the United States District Court for the Northern District of California granted in part and denied in part the Company Defendants motion to dismiss the complaints in the cases referenced above.

On October 8, 2021, Humana Inc. filed a lawsuit in the United States District Court for the Northern District of California against the Company Defendants, Hikma Pharmaceuticals plc, Hikma Pharmaceuticals USA Inc., Hikma Labs, Inc., Eurohealth (USA), Inc., Amneal Pharmaceuticals LLC, Par Pharmaceutical, Inc., Lupin Ltd., Lupin Pharmaceuticals, Inc., and Lupin Inc, raising similar allegations.

On October 8, 2021, Molina Healthcare Inc. filed a lawsuit in the United States District Court for the Northern District of California against the Company Defendants, Hikma Pharmaceuticals plc, Hikma Pharmaceuticals USA Inc., Hikma Labs, Inc., Eurohealth (USA), Inc., Amneal Pharmaceuticals LLC, Par Pharmaceutical, Inc., Lupin Ltd., Lupin Pharmaceuticals, Inc., and Lupin Inc, raising similar allegations.

On February 17, 2022, Health Care Service Corporation filed a lawsuit in the United States District Court for the Northern District of California against the Company Defendants, Hikma Pharmaceuticals plc, Hikma Pharmaceuticals USA Inc., Hikma Labs, Inc., Eurohealth (USA), Inc., Amneal Pharmaceuticals LLC, Par Pharmaceutical, Inc., Lupin Ltd., Lupin Pharmaceuticals, Inc., and Lupin Inc, raising similar allegations.

The parties have submitted a proposed case schedule through briefing on class certification. A trial date will be set following a ruling on class certification.

The plaintiffs in certain of these lawsuits are seeking to represent a class of direct purchasers of Xyrem, and the plaintiffs in the remaining lawsuits are seeking to represent a class of indirect purchasers of Xyrem. Each of the lawsuits generally alleges violations of U.S. federal and state antitrust, consumer protection, and unfair competition laws in connection with the Company Defendants' conduct related to Xyrem, including actions leading up to, and entering into, patent litigation settlement agreements with each of the other named defendants. Each of the lawsuits seeks monetary damages, exemplary damages, equitable relief against the alleged unlawful conduct, including disgorgement of profits and restitution, and injunctive relief. It is possible that additional lawsuits will be filed against the Company Defendants making similar or related allegations. If the plaintiffs were to be successful in their claims, they may be entitled to injunctive relief or we may be required to pay significant monetary damages, which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

GW Acquisition Litigation

On March 15, 2021, GW filed a definitive proxy statement, or Proxy Statement, with the Securities and Exchange Commission in connection with the GW Acquisition.

Since the filing of the Proxy Statement, Jazz Pharmaceuticals plc has been named in two lawsuits filed in state and federal courts in New York on March 17, 2021 by purported GW shareholders in connection with the GW Acquisition. The first was filed in the United States District Court for the Southern District of New York by James Farrell (hereinafter referred to as the Farrell Lawsuit) and an additional suit was filed in New York state court by Brian Levy (hereinafter referred to as the Levy Lawsuit). In addition to Jazz Pharmaceuticals plc, Jazz Pharmaceuticals U.K. Holdings Ltd., GW Pharmaceuticals plc, and the GW Board of Directors are named as defendants in the Farrell Lawsuit. In the Levy Lawsuit, GW Pharmaceuticals plc, the GW Board of Directors, Centerview Partners LLC, and Goldman Sachs & Co. LLC are named as defendants. In addition to the Farrell Lawsuit and the Levy Lawsuit, ten additional suits have been filed in New York, California, and Pennsylvania federal courts by purported GW shareholders against GW Pharmaceuticals plc and its Board of Directors, but which do not name any Jazz Pharmaceuticals parties (hereinafter referred to as the GW Litigation, and collectively with the Farrell Lawsuit and the Levy Lawsuit, as the Transaction Litigation). In the Transaction Litigation, the plaintiffs allege that the Proxy Statement omitted material information and contained misrepresentations, and that the individual members of the GW Board of Directors breached their fiduciary duties, in violation of state and federal laws, including the Securities Exchange Act of 1934. The plaintiffs in the Transaction Litigation sought various remedies, including injunctive relief to prevent the consummation of the GW Acquisition unless certain allegedly material information was disclosed, or in the alternative, rescission or damages.

On April 14, 2021, GW filed a Form 8-K containing supplemental disclosures related to the GW Acquisition. Pursuant to a memorandum of understanding between the parties, the Levy Lawsuit was dismissed on April 14, 2021.

On May 27, 2021, a class action lawsuit was filed in the United States District Court for the Southern District of California by plaintiff Kurt Ziegler against GW and its former Directors asserting claims under Sections 14(a) and 20(a) of the

Securities Exchange Act of 1934, referred to as the Ziegler Lawsuit. The allegations in the Ziegler Lawsuit are similar to those in the previously dismissed Transaction Litigation.

Patent Infringement Litigation

Avadel Patent Litigation

On May 13, 2021, we filed a patent infringement suit against Avadel Pharmaceuticals plc, or Avadel, and several of its corporate affiliates in the United States District Court for the District of Delaware. The suit alleges that Avadel's product candidate FT-218 will infringe five of our patents related to controlled release formulations of oxybate and the safe and effective distribution of oxybate. The suit seeks an injunction to prevent Avadel from launching a product that would infringe these patents, and an award of monetary damages if Avadel does launch an infringing product. Avadel filed an answer to the complaint and counterclaims asserting that the patents are invalid or not enforceable, and that its product, if approved, will not infringe our patents.

On August 4, 2021, we filed an additional patent infringement suit against Avadel in the United States District Court for the District of Delaware. The second suit alleges that Avadel's product candidate FT-218 will infringe a newly-issued patent related to sustained-release formulations of oxybate. The suit seeks an injunction to prevent Avadel from launching a product that would infringe this patent, and an award of monetary damages if Avadel does launch an infringing product. Avadel filed an answer to the complaint and counterclaims asserting that the patents are invalid or not enforceable, and that its product, if approved, will not infringe our patents.

On November 10, 2021, we filed an additional patent infringement suit against Avadel in the United States District Court for the District of Delaware. The third suit alleges that Avadel's product candidate FT-218 will infringe a newly-issued patent related to sustained-release formulations of oxybate. The suit seeks an injunction to prevent Avadel from launching a product that would infringe this patent, and an award of monetary damages if Avadel does launch an infringing product. Avadel filed an answer to the complaint and counterclaims asserting that the patents are invalid or not enforceable, and that its product, if approved, will not infringe our patents.

Canopy Patent Litigation

In December 2020, Canopy Growth Corporation filed a complaint against our subsidiary, GW, in the United States District Court for the Western District of Texas, alleging infringement of its patent, U.S. Patent No. 10,870,632. Canopy claims that our extraction process used to produce material used to produce Epidiolex infringes its patent. Canopy seeks a judgment that we have infringed their patent and an award of monetary damages. In July 2021, we filed an answer to the amended complaint, and counterclaims seeking judgment that the '632 patent is invalid and that we have not infringed the patent. In October 2021, the United States District Court for the Western District of Texas held a claim construction hearing regarding the disputed term of the '632 patent. In November 2021, the Court issued a claim construction order, which the Company views as generally favorable. On February 23, 2022, the parties filed a Joint Motion and Stipulation to Enter Final Judgment in favor of GW. Pursuant to the stipulation, Canopy has the right to appeal the Court's ruling on the disputed term. On February 25, 2022, the Court granted the parties' motion and entered final judgment in favor of GW.

Lupin Patent Litigation

In June 2021, we received notice from Lupin Inc., or Lupin, that it has filed with FDA an ANDA, for a generic version of Xywav. The notice from Lupin included a "paragraph IV certification" with respect to ten of our patents listed in FDA's Orange Book for Xywav on the date of our receipt of the notice. The asserted patents relate generally to the composition and method of use of Xywav, and methods of treatment when Xywav is administered concomitantly with certain other medications. A paragraph IV certification is a certification by a generic applicant that alleges that patents covering the branded product are invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the generic product.

In July 2021, we filed a patent infringement suit against Lupin in the United States District Court for the District of New Jersey. The complaint alleges that by filing its ANDA, Lupin has infringed ten of our Orange Book listed patents. We are seeking a permanent injunction to prevent Lupin from introducing a generic version of Xywav that would infringe our patents. As a result of this lawsuit, we expect that a stay of approval of up to 30 months will be imposed by FDA on Lupin's ANDA. In June 2021, FDA recognized seven years of Orphan Drug Exclusivity for Xywav through July 21, 2027. On October 4, 2021, Lupin filed an answer to the complaint and counterclaims asserting that the patents are invalid or not enforceable, and that its product, if approved, will not infringe our patents.

Otsuka Patent Litigation

In October 2021, Otsuka Pharmaceutical Co., Ltd., or Otsuka, filed claims against GW Pharma Limited and GW Pharmaceuticals Limited, or collectively, the GW Parties, in the English High Court, Patents Court. Otsuka alleges that under a now-expired Research Collaboration and License Agreement between Otsuka and the GW Parties, Otsuka and the GW Parties jointly own certain patents and other intellectual property, that Epidiolex is covered by that intellectual property, and that Otsuka is therefore due a royalty on net sales of Epidiolex.

In December 2021, we filed an application for an order declaring that the English High Court, Patents Court has no jurisdiction over the dispute with Otsuka, or should not exercise its jurisdiction.

In January 2022, we filed a lawsuit against Otsuka in the Supreme Court of the State of New York, County of New York, seeking a declaration that Otsuka is not entitled to any royalties on sales of Epidiolex under the Research Collaboration and License Agreement.

The Company vigorously enforces its intellectual property rights, but cannot predict the outcome of these matters.

From time to time we are involved in legal proceedings arising in the ordinary course of business. We believe there is no other litigation pending that could have, individually or in the aggregate, a material adverse effect on our results of operations or financial condition.

15. Shareholders' Equity

Share Repurchase Program

In November 2016, our board of directors authorized a share repurchase program and as of December 31, 2021 had authorized the repurchase of up to $1.5 billion, exclusive of any brokerage commissions. Under this program, which has no expiration date, we may repurchase ordinary shares from time to time on the open market. The timing and amount of repurchases will depend on a variety of factors, including the price of our ordinary shares, alternative investment opportunities, restrictions under the amended credit agreement, corporate and regulatory requirements and market conditions. The share repurchase program may be modified, suspended or discontinued at any time without prior notice. In 2021, we did not repurchase any of our ordinary shares under the share repurchase program. In 2020, we spent a total of $146.5 million to repurchase 1.2 million of our ordinary shares at an average total purchase price, including brokerage commissions, of $121.98 per share. All ordinary shares repurchased were canceled. As of December 31, 2021, the remaining amount authorized under the share repurchase program was $431.2 million.

Authorized But Unissued Ordinary Shares

We had reserved the following shares of authorized but unissued ordinary shares (in thousands):

	December 31,	
	2021	2020
2011 Equity Incentive Plan	22,195	21,070
2007 Employee Stock Purchase Plan	3,285	2,600
GW Incentive Plans	1,853	—
Amended and Restated 2007 Non-Employee Directors Stock Award Plan	807	889
2007 Equity Incentive Plan	—	5
Total	28,140	24,564

Dividends

In 2021 and 2020, we did not declare or pay cash dividends on our common equity. Under Irish law, dividends may only be paid, and share repurchases and redemptions must generally be funded only out of, "distributable reserves." In addition, the terms of our credit agreement restrict our ability to make certain restricted payments, including dividends and other distributions by us in respect of our ordinary shares, subject to, among other exceptions, (1) a general exception for dividends and restricted payments up to $30 million in the aggregate and (2) an exception that allows for restricted payments, subject to a cap equal to the sum of (i) $100 million plus (ii) so long as our secured leverage ratio (as defined in our credit agreement) does not exceed 3:1 after giving pro forma effect to the restricted payment, a formula-based amount tied to our consolidated net income; provided that such cap applies only if our total leverage ratio (as defined in our credit agreement) exceeds 2:1 after giving pro forma effect to the restricted payment. Any future determination as to the payment of dividends will, subject to Irish legal requirements, be at the sole discretion of our board of directors and will depend on our consolidated financial condition, results of operations, capital requirements, compliance with the terms our credit agreement or other future borrowing arrangements, and other factors our board of directors deems relevant.

16. Comprehensive Income (Loss)

Comprehensive income (loss) includes net income (loss) and all changes in shareholders' equity during a period, except for those changes resulting from investments by shareholders or distributions to shareholders.

Accumulated Other Comprehensive Loss

The components of accumulated other comprehensive loss as of December 31, 2021 and 2020 were as follows (in thousands):

	Net Unrealized Loss From Hedging Activities	Foreign Currency Translation Adjustments	Total Accumulated Other Comprehensive Loss
Balance at December 31, 2020	$ (2,467)	$ (131,885)	$ (134,352)
Other comprehensive income (loss) before reclassifications	(389)	(268,347)	(268,736)
Amounts reclassified from accumulated other comprehensive income (loss)	2,728	—	2,728
Other comprehensive income (loss), net	2,339	(268,347)	(266,008)
Balance at December 31, 2021	$ (128)	$ (400,232)	$ (400,360)

In 2021, other comprehensive loss reflects foreign currency translation adjustments, primarily due to the weakening of the sterling and euro against the U.S. dollar.

17. Net Income (Loss) per Ordinary Share

Basic net income (loss) per ordinary share is based on the weighted-average number of ordinary shares outstanding. Diluted net income (loss) per ordinary share is based on the weighted-average number of ordinary shares outstanding and potentially dilutive ordinary shares outstanding.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS—(Continued)

Basic and diluted net income (loss) per ordinary share were computed as follows (in thousands, except per share amounts):

	Year Ended December 31,		
	2021	2020	2019
Numerator:			
Net income (loss)	$ (329,668)	$ 238,616	$ 523,367
Denominator:			
Weighted-average ordinary shares used in per share calculations - basic	59,694	55,712	56,749
Dilutive effect of employee equity incentive and purchase plans	—	805	801
Weighted-average ordinary shares used in per share calculations - diluted	59,694	56,517	57,550
Net income (loss) per ordinary share :			
Basic	$ (5.52)	$ 4.28	$ 9.22
Diluted	$ (5.52)	$ 4.22	$ 9.09

Potentially dilutive ordinary shares from our employee equity incentive and purchase plans and the Exchangeable Senior Notes are determined by applying the treasury stock method to the assumed exercise of share options, the assumed vesting of outstanding restricted stock units, or RSUs and PRSUs, the assumed issuance of ordinary shares under our employee stock purchase plan, or ESPP, and the assumed issuance of ordinary shares upon exchange of the Exchangeable Senior Notes. The average share price of our ordinary shares in 2021 exceeded the effective exchange price per ordinary share of the 2026 Notes. However, the potential ordinary shares issuable upon exchange were excluded from the calculation of diluted net loss per ordinary share because their effect would have been anti-dilutive. The average price of our ordinary shares in 2021 did not exceed the effective exchange price per ordinary share of the 2021 Notes and 2024 Notes. The potential issue of ordinary shares issuable upon exchange of the Exchangeable Senior Notes had no effect on diluted net income per ordinary share for 2020 and 2019 as the average price of our ordinary shares during those periods did not exceed the effective exchange prices per ordinary share of the Exchangeable Senior Notes.

The following table represents the weighted-average ordinary shares that were excluded from the computation of diluted net income (loss) per ordinary share for the years presented because including them would have an anti-dilutive effect (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Exchangeable Senior Notes	9,725	8,077	5,504
Employee equity incentive and purchase plans	3,927	4,780	5,000

18. Segment and Other Information

Our operating segment is reported in a manner consistent with the internal reporting provided to the chief operating decision maker, or CODM. Our CODM has been identified as our chief executive officer. We have determined that we operate in one business segment, which is the identification, development and commercialization of meaningful pharmaceutical products that address unmet medical needs.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS—(Continued)

The following table presents total long-lived assets by location (in thousands):

	December 31,	
	2021	2020
Ireland	$ 65,478	$ 71,906
United Kingdom	176,778	3,438
United States	76,290	157,282
Italy	16,698	16,008
Other	8,179	8,470
Total long-lived assets (1)	$ 343,423	$ 257,104

(1) Long-lived assets consist of property, plant and equipment and operating lease assets.

19. Revenues

The following table presents a summary of total revenues (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Xyrem	$ 1,265,830	$ 1,741,758	$ 1,642,525
Xywav	535,297	15,264	—
Total Oxybate	1,801,127	1,757,022	1,642,525
Epidiolex/Epidyolex	463,645	—	—
Sunosi	57,914	28,333	3,714
Sativex	12,707	—	—
Total Neuroscience	2,335,393	1,785,355	1,646,239
Zepzelca	246,808	90,380	—
Rylaze	85,629	—	—
Vyxeos	134,060	121,105	121,407
Defitelio/defibrotide	197,931	195,842	172,938
Erwinaze/Erwinase	69,382	147,136	177,465
Total Oncology	733,810	554,463	471,810
Other	9,798	6,842	17,552
Product sales, net	3,079,001	2,346,660	2,135,601
Royalties and contract revenues	15,237	16,907	26,160
Total revenues	$ 3,094,238	$ 2,363,567	$ 2,161,761

The following table presents a summary of total revenues attributed to geographic sources (in thousands):

	Year Ended December 31,		
	2021	2020	2019
United States	$ 2,820,242	$ 2,144,541	$ 1,964,161
Europe	230,158	175,208	150,201
All other	43,838	43,818	47,399
Total revenues	$ 3,094,238	$ 2,363,567	$ 2,161,761

The following table presents a summary of the percentage of total revenues from customers that represented more than 10% of our total revenues:

	Year Ended December 31,		
	2021	2020	2019
ESSDS	60 %	74 %	76 %
McKesson	12 %	12 %	14 %

Financing and payment

Our payment terms vary by the type and location of our customer but payment is generally required in a term ranging from 30 to 45 days.

Contract Liabilities - Deferred Revenue

The deferred revenue balance as of December 31, 2021 primarily related to deferred upfront fees received from Nippon Shinyaku Co., Ltd., or Nippon Shinyaku, in connection with two license, development and commercialization agreements granting Nippon Shinyaku exclusive rights to develop and commercialize each of Defitelio and Vyxeos in Japan. We recognized contract revenues of $2.8 million in 2021 relating to these upfront payments. The deferred revenue balances are being recognized over an average of four years representing the period we expect to perform our research and developments obligations under each agreement.

The following table presents a reconciliation of our beginning and ending balances in contract liabilities from contracts with customers for the year ended December 31, 2021 (in thousands):

	Contract Liabilities
Balance as of December 31, 2020	$ 4,861
Additions	483
Amount recognized within royalties and contract revenues	(2,788)
Balance as of December 31 2021	$ 2,556

20. Share-Based Compensation

GW Incentive Plans

On May 5, 2021, Jazz Pharmaceuticals plc acquired the entire issued share capital of GW Pharmaceuticals plc. In connection with the GW Acquisition, we assumed the GW Pharmaceuticals plc 2008 Long-Term Incentive Plan, GW Pharmaceuticals plc 2017 Long-Term Incentive Plan and GW Pharmaceuticals plc 2020 Long-Term Incentive Plan, each as amended from time to time, together referred to as the GW Incentive Plans. The terms of the GW Incentive Plans provide for the grant of stock options, stock appreciation rights, RSUs, other stock awards, and performance awards that may be settled in cash, shares, or other property. Ordinary shares granted to employees in exchange for GW ADS in connection with the GW Acquisition vest ratably over service periods of two years, while all post-acquisition grants vest ratably over service periods of four years, and expire no more than 10 years after the date of grant. As of December 31, 2021, a total of 1,864,475 of our ordinary shares had been authorized for issuance under the GW Incentive Plans.

2011 Equity Incentive Plan

On January 18, 2012, the businesses of Jazz Pharmaceuticals, Inc. and Azur Pharma were combined in a merger transaction, or the Azur Merger. In connection with the Azur Merger, Jazz Pharmaceuticals, Inc.'s board of directors adopted the 2011 Equity Incentive Plan, or the 2011 Plan, in October 2011 and its stockholders approved the 2011 Plan at the special meeting of the stockholders held in December 2011 in connection with the Azur Merger. The 2011 Plan became effective immediately before the consummation of the Azur Merger and was assumed and adopted by us upon the consummation of the Azur Merger. The terms of the 2011 Plan provide for the grant of stock options, stock appreciation rights, RSUs, other stock awards, and performance awards that may be settled in cash, shares, or other property. All outstanding grants under the 2011 Plan were granted to employees and vest ratably over service periods of four years and expire no more than 10 years after the date of grant. As of December 31, 2021, a total of 32,065,082 of our ordinary shares had been authorized for issuance under the 2011 Plan. In addition, the share reserve under the 2011 Plan will automatically increase on January 1 of each year through January 1, 2022, by the least of (a) 4.5% of the total number of ordinary shares outstanding on December 31 of the preceding calendar year, (b) 5,000,000 shares, or (c) such lesser number of ordinary shares as determined by our board of directors. On January 1, 2022, the share reserve under the 2011 Plan automatically increased by 2,771,906 ordinary shares pursuant to this provision.

2007 Equity Incentive Plan

The 2007 Equity Incentive Plan, or the 2007 Plan, which was initially adopted by the Jazz Pharmaceuticals, Inc. board of directors and approved by the Jazz Pharmaceuticals, Inc. stockholders in connection with its initial public offering, was continued and assumed by us upon consummation of the Azur Merger. The 2007 Plan provided for the grant of stock options, RSUs, stock appreciation rights, performance stock awards and other forms of equity compensation to employees, including

officers, non-employee directors and consultants. Prior to the consummation of the Azur Merger, all of the grants under the 2007 Plan were granted to employees and vest ratably over service periods of three to five years and expire no more than 10 years after the date of grant. Effective as of the closing of the Azur Merger on January 18, 2012, the number of shares reserved for issuance under the 2007 Plan was set to 1,000,000 ordinary shares. The share reserve under the 2007 Plan will not automatically increase. Since the Azur Merger, all of the new grants under the 2007 Plan were granted to non-employee directors, vest ratably over service periods of one to three years and expire no more than 10 years after the date of grant. The 2007 Plan expired in April 2017, and accordingly, no new grants can be awarded under the 2007 Plan. As of December 31, 2021, the number of shares reserved represents issuable shares from options granted but not yet exercised under the 2007 Plan.

2007 Employee Stock Purchase Plan

In 2007, Jazz Pharmaceuticals, Inc.'s employees became eligible to participate in the ESPP. The ESPP was amended and restated by Jazz Pharmaceuticals, Inc.'s board of directors in October 2011 and approved by its stockholders in December 2011. The amended and restated ESPP became effective immediately prior to the effective time of the Azur Merger and was assumed by us upon the consummation of the Azur Merger. The amended and restated ESPP allows our eligible employee participants (including employees of any of a parent or subsidiary company if our board of directors designates such company as eligible to participate) to purchase our ordinary shares at a discount of 15% through payroll deductions. The ESPP consists of a fixed offering period of 24 months with four purchase periods within each offering period. The number of shares available for issuance under our ESPP during any six-month purchase period is 175,000 shares. As of December 31, 2021, a total of 6,105,282 of our ordinary shares had been authorized for issuance under the ESPP. The share reserve under the ESPP will automatically increase on January 1 of each year through January 1, 2022, by the least of (a) 1.5% of the total number of ordinary shares outstanding on December 31 of the preceding calendar year, (b) 1,000,000 shares, and (c) such lesser number of ordinary shares as determined by our board of directors or a duly-authorized committee thereof. On January 1, 2022, the share reserve under the ESPP automatically increased by 923,968 ordinary shares pursuant to this provision.

Amended and Restated 2007 Non-Employee Directors Stock Award Plan

The Amended and Restated 2007 Non-Employee Directors Stock Award Plan, or the 2007 Directors Award Plan, which was initially adopted by the Jazz Pharmaceuticals, Inc. board of directors and approved by the Jazz Pharmaceuticals, Inc. stockholders in connection with its initial public offering, was continued and assumed by us upon the consummation of the Azur Merger. Until October 2011, the 2007 Directors Award Plan provided for the automatic grant of stock options to purchase shares of Jazz Pharmaceuticals, Inc.'s common stock to its non-employee directors initially at the time any individual first became a non-employee director, which vest over three years, and then annually over their period of service on its board of directors, which vest over one year. On October 24, 2011, Jazz Pharmaceuticals, Inc.'s board of directors amended the 2007 Directors Award Plan to eliminate all future initial and annual automatic grants so that future automatic grants would not be made that would be subject to the excise tax imposed by Section 4985 of the Internal Revenue Code of 1986, as amended, or the Internal Revenue Code, in connection with the Azur Merger. Accordingly, all future stock option grants under the 2007 Directors Award Plan will be at the discretion of our board of directors. Since the Azur Merger, all of the new grants under the 2007 Directors Award Plan were granted to non-employee directors and vest ratably over service periods of one to three years and expire no more than 10 years after the date of grant. In addition, the 2007 Directors Award Plan provides the source of shares to fund distributions made prior to August 15, 2010 under the Directors Deferred Compensation Plan described below. In August 2016, our shareholders approved our proposal to expand the types of stock awards that may be granted to our non-employee directors under the 2007 Directors Award Plan and eliminate the final automatic share reserve increase under the 2007 Directors Award Plan that was scheduled to occur on January 1, 2017. In July 2020, our shareholders approved our proposal to increase the number of ordinary shares authorized for issuance under the 2007 Directors Award Plan by 500,000 shares. As of December 31, 2021, a total of 1,403,938 of our ordinary shares had been authorized for issuance under the 2007 Directors Award Plan.

Amended and Restated Directors Deferred Compensation Plan

In May 2007, the Jazz Pharmaceuticals, Inc. board of directors adopted the Directors Deferred Compensation Plan, or the Directors Deferred Plan, which was amended in December 2008 and was then amended and restated in August 2010, and which was continued and assumed by us upon consummation of the Azur Merger. The Directors Deferred Plan allows each non-employee director to elect to defer receipt of all or a portion of his or her annual retainer fees to a future date or dates. Amounts deferred under the Directors Deferred Plan are credited as shares of Jazz Pharmaceuticals, Inc.'s common stock (or our ordinary shares following the Azur Merger) to a phantom stock account, the number of which are based on the amount of the retainer fees deferred divided by the market value of Jazz Pharmaceuticals, Inc.'s common stock (or our ordinary shares following the Azur Merger) on the first trading day of the first open window period following the date the retainer fees are deemed earned. On the 10th business day following the day of separation from the board of directors or the occurrence of a change in control, or

as soon thereafter as practical once the non-employee director has provided the necessary information for electronic deposit of the deferred shares, each non-employee director will receive (or commence receiving, depending upon whether the director has elected to receive distributions from his or her phantom stock account in a lump sum or in installments over time) a distribution of his or her phantom stock account, in our ordinary shares (i) reserved under the 2007 Directors Option Plan prior to August 15, 2010 and (ii) from a new reserve of 200,000 shares set up under the Directors Deferred Plan on August 15, 2010. Since the consummation of the Azur Merger we have not permitted non-employee directors to defer any annual retainer fees under the Directors Deferred Plan. On October 31, 2019, our board of directors approved the termination of the Directors Deferred Plan, and all outstanding phantom stock was distributed to each applicable non-employee director on November 2, 2020. We recorded no expense in 2021, 2020 and 2019 related to retainer fees earned and deferred.

Share-Based Compensation

The table below shows, for market strike price option grants, the weighted-average assumptions used in the Black-Scholes option pricing model and the resulting weighted-average grant date fair value of market strike price option grants granted in each of the past three years:

	Year Ended December 31,		
	2021	2020	2019
Grant date fair value	$ 51.39	$ 34.68	$ 42.09
Volatility	37 %	33 %	32 %
Expected term (years)	4.5	4.6	4.5
Range of risk-free rates	0.4-0.8%	0.2-1.6%	1.3-2.5%
Expected dividend yield	— %	— %	— %

We rely on a blend of the historical and implied volatilities of our own ordinary shares to determine expected volatility for share option grants. In addition, we use a single volatility estimate for each share option grant. The weighted-average volatility is determined by calculating the weighted average of volatilities for all share options granted in a given year.

The expected term of share option grants represents the weighted-average period the awards are expected to remain outstanding and our estimates were based on historical exercise data. The risk-free interest rate assumption was based on zero coupon U.S. Treasury instruments whose term was consistent with the expected term of our share option grants. The expected dividend yield assumption was based on our history and expectation of dividend payouts.

Share-based compensation expense related to share options, RSUs, PRSUs and grants under our ESPP was as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Selling, general and administrative	$ 135,285	$ 84,384	$ 78,697
Research and development	43,758	29,242	25,229
Cost of product sales	9,963	7,372	6,637
Total share-based compensation expense, pre-tax	189,006	120,998	110,563
Income tax benefit from share-based compensation expense	(33,958)	(12,838)	(15,712)
Total share-based compensation expense, net of tax	$ 155,048	$ 108,160	$ 94,851

We recognized income tax benefits related to share option exercises of $9.3 million, $3.9 million and $5.1 million in 2021, 2020 and 2019, respectively.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS—(Continued)

Share Options

The following table summarizes information as of December 31, 2021 and activity during 2021 related to our share option plans:

	Shares Subject to Outstanding Options (In thousands)	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value (In thousands)
Outstanding at January 1, 2021	5,279	$ 130.51		
Options granted	110	164.45		
Options exercised	(1,041)	114.33		
Options forfeited	(137)	139.24		
Options expired	(90)	164.45		
Outstanding at December 31, 2021	4,121	$ 134.48	5.6	$ 30,696
Vested and expected to vest at December 31, 2021	4,039	$ 134.56	5.6	$ 30,164
Exercisable at December 31, 2021	3,270	$ 135.06	5.1	$ 26,248

Aggregate intrinsic value shown in the table above is equal to the difference between the exercise price of the underlying share options and the fair value of our ordinary shares for share options that were in the money. The aggregate intrinsic value changes based on the fair market value of our ordinary shares. The aggregate intrinsic value of share options exercised was $51.8 million, $26.4 million and $26.2 million during 2021, 2020 and 2019, respectively. We issued new ordinary shares upon exercise of share options.

As of December 31, 2021, total compensation cost not yet recognized related to unvested share options was $29.2 million, which is expected to be recognized over a weighted-average period of 1.8 years.

As of December 31, 2021, total compensation cost not yet recognized related to grants under the ESPP was $4.4 million, which is expected to be recognized over a weighted-average period of 1.1 years.

Nominal Strike Price Options

During the second quarter of 2021, we issued nominal strike price options to replace certain unvested GW awards in connection with the GW Acquisition with a weighted-average grant date fair value of $170.82. The fair value of nominal strike price options was determined on the date of the grant based on the market price of our ordinary shares as of that date.

The following table summarizes information as of December 31, 2021 and activity during 2021 related to our nominal strike price options:

	Shares Subject to Outstanding Options (In thousands)	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value (In thousands)
Outstanding at January 1, 2021	—	$ —		
Options granted	124	0.02		
Options exercised	(1)	0.02		
Options forfeited	(7)	0.02		
Outstanding at December 31, 2021	116	$ 0.02	7.4	$ 14,803
Vested and expected to vest at December 31, 2021	110	$ 0.02	7.3	$ 13,969
Exercisable at December 31, 2021	22	$ 0.02	0.5	$ 2,846

As of December 31, 2021, total compensation cost not yet recognized related to unvested nominal strike price options was $8.1 million, which is expected to be recognized over a weighted-average period of 1.1 years.

Restricted Stock Units

In 2021, we granted RSUs covering an equal number of our ordinary shares to employees with a weighted-average grant date fair value of $168.10. The fair value of RSUs is determined on the date of grant based on the market price of our ordinary shares as of that date. The fair value of the RSUs is recognized as an expense ratably over the vesting period of four years. In 2021, 692,000 RSUs were released with 465,000 ordinary shares issued and 227,000 ordinary shares withheld for tax purposes.

The total fair value of shares vested was $109.2 million, $53.5 million and $52.0 million during 2021, 2020 and 2019, respectively.

As of December 31, 2021, total compensation cost not yet recognized related to unvested RSUs was $238.2 million, which is expected to be recognized over a weighted-average period of 2.6 years.

The following table summarizes information as of December 31, 2021 and activity during 2021 related to our RSUs:

	Number of RSUs (In thousands)	Weighted-Average Grant-Date Fair Value	Weighted-Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value (In thousands)
Outstanding at January 1, 2021	1,878	$ 125.07		
RSUs granted	1,780	168.10		
RSUs released	(692)	133.40		
RSUs forfeited	(335)	148.12		
Outstanding at December 31, 2021	2,631	$ 149.05	1.4	$ 335,224

Performance-Based Restricted Stock Units

In May 2021, the Compensation & Management Development Committee of our board of directors approved awards of PRSU's to certain employees of the Company, subject to vesting on the achievement of certain commercial and pipeline performance criteria to be assessed over a performance period from the date of the grant to December 31, 2023. Following the determination of the Company's achievement with respect to the performance criteria, the amount of shares awarded will be subject to adjustment based on the application of a relative TSR modifier. The number of shares that may be earned ranges between 0% and 200% of the target number of PRSUs granted based on the degree of achievement of the applicable performance metric and the application of the relative TSR modifier.

The table below shows the number of PRSUs granted covering an equal number of our ordinary shares and the weighted-average grant date fair value of PRSUs granted:

	Number of PRSUs (In thousands)	Weighted-Average Grant-Date Fair Value	Weighted-Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value (In thousands)
Outstanding at January 1, 2021	—	$ —		
PRSUs granted	224	190.81		
PRSUs forfeited	(10)	190.81		
Outstanding at December 31, 2021	214	$ 190.81	2.0	$ 27,265

As of December 31, 2021, total compensation cost not yet recognized related to unvested PRSUs was $26.4 million, which is expected to be recognized over a weighted-average period of 2.0 years.

As the PRSUs granted in May 2021 are subject to a market condition, the grant date fair value for such PRSUs was based on a Monte Carlo simulation model. The Company evaluated the performance targets in the context of its current long-range financial plan and its product candidate development pipeline and recognized compensation expense based on the probable number of awards that will ultimately vest.

21. Employee Benefit Plans

We maintain a qualified 401(k) savings plan, in which all U.S. based employees are eligible to participate, provided they meet the requirements of the plan. We match certain employee contributions under the 401(k) savings plan and for the years ended December 31, 2021, 2020 and 2019 we recorded expense of $9.1 million, $6.3 million and $5.0 million, respectively, related to this plan.

We also operate a number of defined contribution retirement plans for certain non-U.S. based employees. Expenses related to contributions to such plans for the years ended December 31, 2021, 2020 and 2019 were $11.4 million, $4.2 million and $3.2 million, respectively.

The expense for employee benefit plans in 2021 included plans acquired in the GW Acquisition.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS—(Continued)

22. Income Taxes

The components of income (loss) before income tax expense (benefit) and equity in loss of investees were as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Ireland	$ 97,557	$ (102,328)	$ (6,451)
United Kingdom	(681,291)	3,836	3,304
United States	221,185	372,910	317,728
Other	249,711	677	139,721
Total	$ (112,838)	$ 275,095	$ 454,302

The following table sets forth the details of income tax expense (benefit) (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Current			
Ireland	$ 25,770	$ 19,437	$ 51,696
United Kingdom	(924)	166	—
United States	88,850	110,896	109,495
Other	33,222	39,955	2,265
Total current tax expense	146,918	170,454	163,456
Deferred, exclusive of other components below			
Ireland	(5,388)	(32,458)	(163,626)
United Kingdom	(111,534)	679	1,353
United States	(46,531)	(29,117)	(41,297)
Other	(28,604)	(74,278)	(38,597)
Total deferred, exclusive of other components	(192,057)	(135,174)	(242,167)
Deferred, change in tax rates			
United Kingdom	259,873	(1,155)	(52)
United States	1,377	(371)	203
Other	5	(237)	5,406
Total deferred, change in tax rates	261,255	(1,763)	5,557
Total deferred tax expense (benefit)	69,198	(136,937)	(236,610)
Total income tax expense (benefit)	$ 216,116	$ 33,517	$ (73,154)

Our income tax expense of $216.1 million and $33.5 million in 2021 and 2020, respectively, and our income tax benefit of $73.2 million in 2019 related to tax arising on income in Ireland, the U.K., the U.S. and certain other foreign jurisdictions, certain unrecognized tax benefits and various expenses not deductible for income tax purposes. Our income tax expense in 2021 included an expense of $259.9 million arising on the remeasurement of our U.K. net deferred tax liability, which arose primarily in relation to the GW Acquisition, due to a change in the statutory tax rate in the U.K. following enactment of the U.K. Finance Act 2021. Our income tax benefit in 2019 included a discrete tax benefit of $112.3 million resulting from an intra-entity intellectual property asset transfer.

The effective tax rates for 2021, 2020 and 2019 were (191.5)% , 12.2% and (16.1)%, respectively. The effective tax rate for 2021 was lower than the Irish statutory rate of 12.5% primarily due to the impact of the remeasurement of our U.K. net deferred tax liability due to the change in the statutory tax rate in the U.K. The effective tax rate for 2020 was lower than the Irish statutory rate of 12.5% primarily due to the impact of originating tax credits and deductions on subsidiary equity, partially offset by income taxable at a rate higher than the Irish statutory rate, the disallowance of certain interest deductions and a provision for a proposed settlement reached with the French taxing authorities. The effective tax rate for 2019 was lower than the Irish statutory rate of 12.5% primarily due to the impact of the intra-entity intellectual property asset transfer. The decrease in the effective tax rate in 2021 compared to 2020 was primarily due to the impact of the U.K. statutory rate change. Excluding this impact, the increase in the benefit for income taxes in 2021 compared to 2020 resulted primarily from the mix of pre-tax income and losses incurred across tax jurisdictions, deductions on subsidiary equity and the impacts recognized in 2020 of the

disallowance of certain interest deductions and a provision for a proposed settlement reached with the French taxing authorities. The increase in the effective tax rate in 2020 compared to 2019 was primarily due to the impact of the intra-entity intellectual property asset transfer. Excluding this effect, the increase in the effective tax rate for 2020 compared to 2019 was primarily due to the benefit recognized in 2019 from the application of the Italian patent box incentive regime 2015 through 2019 and the impacts recognized in 2020 of the disallowance of certain interest deductions and a provision for a proposed settlement reached with the French taxing authorities.

The reconciliation between the statutory income tax rate applied to income before the income tax expense (benefit) and equity in loss of investees and our effective income tax rate was as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Income tax expense/(benefit) at the statutory income tax rate	$ (14,105)	$ 34,387	$ 56,788
Change in tax rate	261,663	(1,836)	6,923
Deduction on subsidiary equity	(116,438)	(25,740)	(23,450)
Change in valuation allowance	81,280	6,074	14,823
Research and other tax credits	(31,069)	(30,836)	(39,776)
Non-deductible acquisition-related costs	20,929	—	11,738
Non-deductible compensation	19,914	8,604	8,321
Financing costs	14,418	7,132	(7,615)
Change in unrecognized tax benefits	(6,436)	16,309	499
Tax deficiencies/(excess tax benefits) from share-based compensation	(5,555)	5,274	537
Foreign income tax rate differential	(4,343)	16,126	39,695
Foreign derived intangible income benefit	(3,416)	—	—
Change in estimates	(2,653)	(3,604)	1,156
Intra-entity transfer of intellectual property assets	—	—	(112,274)
Patent box incentive benefit	—	—	(31,642)
Other	1,927	1,627	1,123
Reported income tax expense/(benefit)	$ 216,116	$ 33,517	$ (73,154)

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS—(Continued)

Significant components of our net deferred tax assets/(liabilities) were as follows (in thousands):

	December 31,	
	2021	2020
Deferred tax assets:		
Tax credit carryforwards	$ 284,155	$ 258,296
Operating loss carryforwards	265,156	68,860
Intangible assets	189,959	173,918
Accrued liabilities	84,509	62,561
Deduction on subsidiary equity carryforwards	78,514	13,201
Indirect effects of unrecognized tax benefits	46,876	48,743
Share-based compensation	37,289	26,090
Lease liabilities	15,865	31,787
Other	65,224	69,289
Total deferred tax assets	1,067,547	752,745
Valuation allowance	(154,255)	(77,342)
Deferred tax assets, net of valuation allowance	913,292	675,403
Deferred tax liabilities:		
Intangible assets	(1,652,297)	(448,310)
Inventory	(181,742)	—
Operating lease assets	(12,657)	(26,316)
Other	(56,034)	(76,258)
Total deferred tax liabilities	(1,902,730)	(550,884)
Net of deferred tax assets and (liabilities)	$ (989,438)	$ 124,519

The net change in valuation allowance was an increase of $76.9 million, $11.0 million and $5.1 million in 2021, 2020 and 2019, respectively.

The following table summarizes the presentation of deferred tax assets and liabilities (in thousands):

	December 31,	
	2021	2020
Deferred tax assets	$ 311,103	$ 254,916
Deferred tax liabilities	(1,300,541)	(130,397)
Net of deferred tax assets and (liabilities)	$ (989,438)	$ 124,519

As of December 31, 2021, we had net operating losses, or NOL, carryforwards and tax credit carryforwards for U.S. federal income tax purposes of approximately $81.6 million and $216.5 million, respectively, available to reduce future income subject to income taxes. The U.S. federal NOL carryforwards will expire, if not utilized, in the tax years 2022 to 2036, and the U.S. federal tax credits will expire, if not utilized, in the tax years 2022 to 2041. In addition, we had approximately $44.3 million of NOL carryforwards and $8.0 million of tax credit carryforwards as of December 31, 2021 available to reduce future taxable income for U.S. state income tax purposes. The U.S. state NOL carryforwards will expire, if not utilized, in the tax years 2022 to 2040. As of December 31, 2021, there were NOL and other carryforwards for income tax purposes of approximately $864.9 million, $224.3 million, $133.5 million and $45.7 million available to reduce future income subject to income taxes in the United Kingdom, Malta, Ireland and Luxembourg respectively. The NOLs and other carryforwards generated in the United Kingdom, Malta, Ireland and Luxembourg have no expiration date. We also had foreign tax credit carryforwards in Ireland, as of December 31, 2021, of $58.8 million, which may only be utilized against certain sources of income. The foreign tax credit carryforwards have no expiration date.

Utilization of certain of our NOL and tax credit carryforwards in the U.S. is subject to an annual limitation due to the ownership change limitations provided by Sections 382 and 383 of the Internal Revenue Code and similar state provisions. Such an annual limitation may result in the expiration of certain NOLs and tax credits before future utilization. In addition, as a result of the Azur Merger, until 2022 we are subject to certain limitations under the Internal Revenue Code in relation to the utilization of U.S. NOLs to offset U.S. taxable income resulting from certain transactions.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS—(Continued)

Valuation allowances require an assessment of both positive and negative evidence when determining whether it is more likely than not that deferred tax assets are recoverable. Such assessment is required by tax paying component. Our valuation allowance was $154.3 million and $77.3 million as of December 31, 2021 and 2020, respectively, for certain Irish, U.S. (federal and state) and foreign deferred tax assets which we maintain until sufficient positive evidence exists to support reversal. During 2021, as part of the overall change in valuation allowance, we recognized a net income tax expense of $81.3 million relating primarily to the creation of a valuation allowance against certain deferred tax assets primarily associated with temporary differences related to foreign subsidiaries and foreign tax credit carryforwards. During 2020, as part of the overall change in valuation allowance, we recognized a net income tax expense of $6.2 million relating primarily to the creation of a valuation allowance against certain deferred tax assets primarily associated with temporary differences related to foreign subsidiaries. During 2019, as part of the overall change in valuation allowance, we recognized a net income tax expense of $6.3 million relating primarily to the creation of a valuation allowance of $15.7 million against certain deferred tax assets primarily associated with foreign tax credits and temporary differences related to foreign subsidiaries, partially offset by the net release of valuation allowances against certain deferred tax assets primarily associated with NOLs. We periodically evaluate the likelihood of the realization of deferred tax assets and will adjust such amounts in light of changing facts and circumstances including, but not limited to, future projections of taxable income, tax legislation, rulings by relevant taxing authorities, the progress of tax examinations and the regulatory approval of products currently under development. Realization of the deferred tax assets is dependent on future taxable income.

No provision has been made for income tax on undistributed earnings of the Company's foreign subsidiaries where such earnings are considered indefinitely reinvested in the foreign operations. Temporary differences related to such earnings totaled approximately $2.3 billion as of December 31, 2021. In the event of the distribution of those earnings in the form of dividends, a sale of the subsidiaries, or certain other transactions, we may be liable for income taxes, subject to an adjustment, if any, for foreign tax credits. The Company estimates that it would incur additional income taxes of up to approximately $113 million on repatriation of these unremitted earnings to Ireland.

We only recognize the financial statement effects of a tax position when it is more likely than not, based on the technical merits, that the position will be sustained upon examination. As a result, we have recorded an unrecognized tax benefit for certain tax benefits which we judge may not be sustained upon examination.

A reconciliation of our gross unrecognized tax benefits follows (in thousands):

	December 31,		
	2021	2020	2019
Balance at the beginning of the year	$ 146,557	$ 124,319	$ 118,213
Increases related to current year tax positions	26,675	27,908	27,552
Increases related to prior year tax positions	211	19,712	761
Decreases related to prior year tax positions	(182)	(213)	(91)
Increases recognized through purchase accounting	5,916	—	—
Decreases related to settlements with taxing authorities	(14,744)	—	—
Lapse of the applicable statute of limitations	(26,566)	(25,169)	(22,116)
Balance at the end of the year	$ 137,867	$ 146,557	$ 124,319

The unrecognized tax benefits were included in income taxes payable, other non-current liabilities and deferred tax assets, net, in our consolidated balance sheets. Interest related to our unrecognized tax benefits is recorded in the income tax expense (benefit) in our consolidated statements of income (loss). As of December 31, 2021 and 2020, our accrued interest and penalties related to income taxes was $4.6 million and $11.3 million, respectively. Interest and penalties related to income taxes benefits recognized in the consolidated statements of income (loss) were not significant. Included in the balance of unrecognized tax benefits were potential benefits of $82.0 million and $93.0 million at December 31, 2021 and 2020, respectively, that, if recognized, would affect the effective tax rate on income.

We file income tax returns in multiple tax jurisdictions, the most significant of which are Ireland the U.K. and the U.S. (both at the federal level and in various state jurisdictions). For Ireland we are no longer subject to income tax examinations by taxing authorities for the years prior to 2017. For the U.K. we are no longer subject to income tax examinations by taxing authorities for the years prior to 2018. The U.S. jurisdictions generally have statute of limitations three to four years from the later of the return due date or the date when the return was filed. However, in the U.S. (at the federal level and in most states), carryforwards that were generated in 2017 and earlier may still be adjusted upon examination by the taxing authorities. During 2021, certain of our subsidiaries were under examination by the French taxing authorities for the years ended December 31, 2012, 2013, 2015, 2016 and 2017. Due to the subjective nature of the transfer pricing issues involved, the

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS—(Continued)

Company reached an agreement with the French taxing authorities to settle the examinations for all open years. The Company paid incremental taxes, interest and penalties of $19.7 million, during 2021 to close all periods under examination. Certain of our Italian subsidiaries are currently under examination by the Italian taxing authorities for the year ended December 31, 2017. Certain of our Luxembourg subsidiaries are currently under examination by the Luxembourg taxing authorities for the years ended December 31, 2017 and 2018. Certain of our German subsidiaries are currently under examination by the German taxing authorities for the years ended December 31, 2017, 2018 and 2019.

Schedule II

Valuation and Qualifying Accounts
(In thousands)

		Balance at beginning of period	Additions charged to costs and expenses	Other Additions	Deductions	Balance at end of period
For the year ended December 31, 2021						
Allowance for doubtful accounts	(1)	$ 50	$ 127	$ 771	$ (650)	$ 298
Allowance for sales discounts	(1)	144	13,196	1,243	(12,457)	2,126
Allowance for chargebacks	(1)	5,293	91,425	1,322	(86,651)	11,389
Deferred tax asset valuation allowance	(2)(3)(4)	77,342	82,820	9	(5,916)	154,255
For the year ended December 31, 2020						
Allowance for doubtful accounts	(1)	$ 50	$ 5	$ —	$ (5)	$ 50
Allowance for sales discounts	(1)	113	1,432	—	(1,401)	144
Allowance for chargebacks	(1)	1,133	45,550	—	(41,390)	5,293
Deferred tax asset valuation allowance	(2)(3)(4)	66,307	6,576	4,961	(502)	77,342
For the year ended December 31, 2019						
Allowance for doubtful accounts	(1)	$ 50	$ 9	$ —	$ (9)	$ 50
Allowance for sales discounts	(1)	76	782	—	(745)	113
Allowance for chargebacks	(1)	408	41,864	—	(41,139)	1,133
Deferred tax asset valuation allowance	(2)(3)	61,237	20,086	357	(15,373)	66,307

(1) Shown as a reduction of accounts receivable. Charges related to sales discounts and chargebacks are reflected as a reduction of revenue.

(2) Additions to the deferred tax asset valuation allowance charged to costs and expenses relate to movements on certain Irish, U.S. (federal and state) and other foreign deferred tax assets where we continue to maintain a valuation allowance until sufficient positive evidence exists to support reversal.

(3) Other additions to the deferred tax asset valuation allowance relate to currency translation adjustments recorded directly in other comprehensive income and, in 2019, additions resulting from the Cavion asset acquisition.

(4) Deductions from the deferred tax asset valuation allowance include movements relating to utilization of NOLs and tax credit carryforwards, release in valuation allowance and other movements including adjustments following finalization of tax returns.

Exhibit 4.6

DESCRIPTION OF SHARE CAPITAL

The following description of the share capital of Jazz Pharmaceuticals plc, or the Company, is a summary. This summary does not purport to be complete and is qualified in its entirety by reference to the Irish Companies Act 2014 (as amended), or the Companies Act, and the complete text of the Company's amended and restated memorandum and articles of association, which amended and restated memorandum and articles of association, or the Company's Constitution, are filed as Exhibit 3.1 to the Company's Quarterly Report on Form 10-Q filed with the U.S. Securities and Exchange Commission, or SEC, on August 9, 2016. You should read those laws and documents carefully.

Capital Structure

Authorized Share Capital

The authorized share capital of the Company is €40,000 and $30,000, divided into 4,000,000 non-voting euro deferred shares with nominal value of €0.01 per share and 300,000,000 ordinary shares with nominal value of $0.0001 per share.

The Company may issue shares subject to the maximum authorized share capital contained in the Company's Constitution. The authorized share capital may be increased or reduced (but not below the number of shares then issued and outstanding) by a resolution approved by a simple majority of the votes cast at a general meeting, in person or by proxy, of the Company's shareholders (referred to under Irish law as an "ordinary resolution"). The shares comprising the Company's authorized share capital may be divided into shares of such nominal value as the resolution shall prescribe. As a matter of Irish law, the directors of a company may issue new ordinary or preferred shares for cash without shareholder approval once authorized to do so by the memorandum and articles of association or by an ordinary resolution adopted by the shareholders at a general meeting. The authorization may be granted for a maximum period of five years, at which point it must be renewed by the shareholders by an ordinary resolution.

The Company's board of directors is authorized pursuant to shareholder resolutions passed on July 29, 2021 to issue new ordinary or preferred shares for cash without shareholder approval for a period of five years from the date of the passing of the resolutions.

The rights and restrictions to which ordinary shares are subject are prescribed in the Company's Constitution. The Company's Constitution permits it to issue preferred shares once authorized to do so by ordinary resolution. The Company may, by ordinary resolution and without obtaining any vote or consent of the holders of any class or series of shares, unless expressly provided by the terms of that class or series of shares, provide from time to time for the issuance of other classes or series of shares and to establish the characteristics of each class or series, including the number of shares, designations, relative voting rights, dividend rights, liquidation and other rights, redemption, repurchase or exchange rights and any other preferences and relative, participating, optional or other rights and limitations not inconsistent with applicable law.

Irish law does not recognize fractional shares held of record. Accordingly, the Company's Constitution does not provide for the issuance of fractional shares, and the official Irish register of the Company will not reflect any fractional shares. Whenever an alteration or reorganization of the Company's share capital would result in any shareholder becoming entitled to fractions of a share, the Company's board of directors may, on behalf of those shareholders that would become entitled to fractions of a share, sell the shares representing the fractions for the best price reasonably obtainable, to any person and distribute the proceeds of the sale in due proportion among those members.

Issued Share Capital

As of December 31, 2021, 61,597,929 ordinary shares were issued and outstanding. In addition, as of December 31, 2021, 4,000,000 non-voting euro deferred shares were issued and outstanding at that time, which shares are held by nominees in order to satisfy an Irish legislative requirement to maintain a minimum level of issued share capital denominated in euro. The euro deferred shares, which are not listed on any stock exchange and are not the subject of any registration, carry no voting rights and are not entitled to receive any dividend or distribution. On a return of assets, whether on liquidation or otherwise, the euro deferred shares will entitle the holder thereof only to the repayment of the amounts paid up on such shares after repayment of the capital paid up on ordinary shares plus the payment of $5,000,000 on each of the ordinary shares and the holders of the euro deferred shares (as such) will not be entitled to any further participation in the assets or profits of the Company.

Preemption Rights, Share Warrants and Share Options

Under Irish law, certain statutory preemption rights apply automatically in favor of shareholders where shares are to be issued for cash. However, the Company has opted out of these preemption rights by way of shareholder resolution as permitted under Irish law. Irish law provides that this opt-out expires every five years unless renewed by a resolution approved by not less than 75% of the votes cast at a general meeting, in person or by proxy, of the Company's shareholders (referred to under Irish law as a "special resolution"). The Company's current opt-out was approved by shareholder resolutions passed at an extraordinary general meeting on September 23, 2021 (the "**EGM**") and is limited to the allotment of equity securities up to an aggregate nominal value of US$613.60 (6,136,036 shares) (being equivalent to approximately 10% of the aggregate nominal value of the Company's issued ordinary share capital as at the last practicable date prior to the issue of the notice of the EGM) and provided further that, with respect to equity securities up to an aggregate nominal value of US$306.80 (3,068,018 shares) (being equivalent to approximately 5% of the aggregate nominal value of the Company's issued ordinary share capital as at the last practicable date prior to the issue of the notice of the EGM), such allotments are to be used only for the purposes of financing (or refinancing, if the allotment is announced within six months after the original transaction) a transaction which the board of directors of the Company determines to be an acquisition or specified capital investment. This opt-out will expire on March 23, 2023 and if it is not renewed before that date, shares issued for cash will need to be offered to existing shareholders on a pro rata basis to their existing shareholding before the shares may be issued to any new shareholders. The statutory preemption rights do not apply (i) where shares are issued for non-cash consideration (such as in a stock-for-stock acquisition), (ii) to the issue of non-equity shares (that is, shares that have the right to participate only up to a specified amount in any income or capital distribution) or (iii) where shares are issued pursuant to an employee stock option or similar equity plan.

The Company's Constitution provides that, subject to any shareholder approval requirement under any laws, regulations or the rules of any stock exchange to which it is subject, the Company's board of directors is authorized, from time to time, in its discretion, to grant such persons, for such periods and upon such terms as it deems advisable, options to purchase such number of shares of any class or classes or of any series of any class as the Company's board of directors may deem advisable, and to cause warrants or other appropriate instruments evidencing such options to be issued. The Companies Act provides that, save to the extent the constitution of a company provides otherwise, the directors of a company may issue options. The Company is subject to the rules of The NASDAQ Stock Market LLC and the U.S. Internal Revenue Code of 1986, or the Code, which require shareholder approval of certain equity plan and share issuances. The Company's board of directors may issue shares upon exercise of validly issued warrants or options without shareholder approval or authorization, except as described above (up to the relevant authorized share capital limit).

Dividends

Under Irish law, dividends and distributions may only be made from distributable reserves. Distributable reserves generally means accumulated realized profits less accumulated realized losses and includes reserves created by way of capital reduction. In addition, no distribution or dividend may be made unless the Company's net

assets are equal to, or in excess of, the aggregate of its called up share capital plus undistributable reserves and the distribution does not reduce its net assets below such aggregate. Undistributable reserves include the share premium account, the par value of shares acquired by the Company and the amount by which the Company's accumulated unrealized profits, so far as not previously utilized by any capitalization, exceed the Company's accumulated unrealized losses, so far as not previously written off in a reduction or reorganization of capital.

The determination as to whether or not the Company has sufficient distributable reserves to fund a dividend must be made by reference to its "relevant financial statements." The "relevant financial statements" are either the last set of unconsolidated annual audited financial statements or other financial statements properly prepared in accordance with the Companies Act, which give a "true and fair view" of the Company's unconsolidated financial position and accord with accepted accounting practice. The relevant financial statements must be filed in the Companies Registration Office (the official public registry for companies in Ireland).

The Company's Constitution authorizes the directors to declare dividends without shareholder approval to the extent they appear justified by profits lawfully available for distribution. The Company's board of directors may also recommend a dividend to be approved and declared by the shareholders at a general meeting. The Company's board of directors may direct that the payment be made by distribution of assets, shares or cash, and no dividend issued may exceed the amount recommended by the directors. The dividends declared by the directors or shareholders may be paid in the form of cash or non-cash assets and may be paid in dollars or any other currency.

The Company's board of directors may deduct from any dividend payable to any shareholder any amounts payable by such shareholder to the Company in relation to its shares.

The Company may issue shares with preferred rights to participate in dividends declared by the Company from time to time, as determined by ordinary resolution. The holders of preferred shares may, depending on their terms, rank senior to ordinary shares in terms of dividend rights and/or be entitled to claim arrears of a declared dividend out of subsequently declared dividends in priority to ordinary shareholders.

Share Repurchases, Redemptions and Conversions

Overview

The Company's Constitution provides that, unless the board specifically determines otherwise, any ordinary share that it has agreed to acquire shall be deemed to be a redeemable share. Accordingly, for Irish law purposes, the repurchase of ordinary shares by the Company may technically be effected as a redemption of those shares as described below under "*—Repurchases and Redemptions*." If the Company's Constitution did not contain such provision, repurchases by the Company would be subject to many of the same rules that apply to purchases of its ordinary shares by subsidiaries described below under "*—Purchases by the Company's Subsidiaries*," including the shareholder approval requirements described below, and the requirement that any purchases on market be effected on a "recognized stock exchange," which, for purposes of the Companies Act, includes The NASDAQ Global Select Market. Neither Irish law nor any of the Company's constituent documents places limitations on the right of nonresident or foreign owners to vote or hold its ordinary shares. Except where otherwise noted, references herein to repurchasing or buying back ordinary shares refer to the redemption of ordinary shares by the Company or the purchase of ordinary shares by one of its subsidiaries, in each case in accordance with the Company's Constitution and Irish law as described below.

Repurchases and Redemptions

Under Irish law, a company may issue redeemable shares and redeem them out of distributable reserves or the proceeds of a new issue of shares for that purpose. Please see also "*—Dividends*." The Company may not purchase any of its shares if, as a result of such purchase, the nominal value of its issued share capital which is not redeemable would be less than 10% of the nominal value of its total issued share capital. All redeemable shares

must also be fully-paid. Redeemable shares may, upon redemption, be cancelled or held in treasury. Based on the provisions of the Company's Constitution, shareholder approval will not be required to redeem its shares.

The Company may also be given an additional general authority to purchase its ordinary shares on market by way of ordinary resolution, which would take effect on the same terms and be subject to the same conditions as applicable to purchases by the Company's subsidiaries as described below.

Repurchased and redeemed shares may be cancelled or held as treasury shares. The nominal value of treasury shares held by the Company at any time must not exceed 10% of the aggregate of the par value and share premium received in respect of the allotment of the Company shares together with the par value of any shares acquired by the Company. The Company may not exercise any voting rights in respect of any shares held as treasury shares.

Treasury shares may be canceled by the Company or re-issued subject to certain conditions.

Purchases by the Company's Subsidiaries

Under Irish law, an Irish or non-Irish subsidiary of the Company may purchase the Company's shares either on market or off market. For a subsidiary of the Company to make purchases on market of ordinary shares, the Company's shareholders must provide general authorization for such purchase by way of ordinary resolution. However, as long as this general authority has been granted, no specific shareholder authority for a particular on market purchase by a subsidiary of ordinary shares is required. For a purchase of ordinary shares by a subsidiary of the Company off market, the proposed purchase contract must be authorized by special resolution of the Company's shareholders before the contract is entered into. The person whose ordinary shares are to be bought back cannot vote in favor of the special resolution and, from the date of the notice of the meeting at which the resolution approving the contract is proposed, the purchase contract must be on display or must be available for inspection by the Company's shareholders at the registered office of the Company.

In order for one of the Company's subsidiaries to make an on market purchase of its shares, such shares must be purchased on a "recognized stock exchange." The NASDAQ Global Select Market, on which ordinary shares are currently listed, is specified as a recognized stock exchange for this purpose by Irish law.

The number of shares held by the Company's subsidiaries at any time will count as treasury shares and will be included in any calculation of the permitted treasury share threshold of 10% of the aggregate of the par value and share premium received in respect of the allotment of the Company shares together with the par value of any shares acquired by the Company. While a subsidiary holds the Company's shares, it cannot exercise any voting rights in respect of those shares and no dividend or other payment (including any payment in a winding up of the Company) shall be payable in respect of those shares. The acquisition of ordinary shares by a subsidiary must be funded out of distributable reserves of the subsidiary.

Lien on Shares, Calls on Shares and Forfeiture of Shares

The Company's Constitution provides that it has a first and paramount lien on every share that is not a fully paid up share for all amounts payable at a fixed time or called in respect of that share. Subject to the terms of their allotment, directors may call for any unpaid amounts in respect of any shares to be paid, and if payment is not made, the shares may be forfeited. These provisions are standard inclusions in the memorandum and articles of association of an Irish public company limited by shares such as the Company's and are only applicable to ordinary shares that have not been fully paid up.

Bonus Shares

Under the Company's Constitution, the Company's board of directors may resolve to capitalize any amount for the time being standing to the credit of any of the Company's reserve accounts or to the credit of the profit and loss

account which is not available for distribution through the issuance of fully paid up bonus shares on the same basis of entitlement as would apply in respect of a dividend distribution.

Consolidation and Division; Subdivision

Under the Company's Constitution, the Company may, by ordinary resolution, consolidate and divide all or any of its share capital into shares of larger nominal value than its existing shares or subdivide its shares into smaller amounts than are fixed by the Company's Constitution.

Reduction of Share Capital

The Company may, by ordinary resolution, reduce its authorized share capital in any way. The Company also may, by special resolution and subject to confirmation by the Irish High Court, reduce or cancel its issued share capital (which includes share premium) in any manner permitted by the Companies Act.

Annual Meetings of Shareholders

The Company is required to hold an annual general meeting at intervals of no more than 15 months from the previous annual general meeting, provided that an annual general meeting is held in each calendar year following the first annual general meeting and no more than nine months after the Company's fiscal year-end. The Company's articles of association provide that shareholder meetings may be held outside of Ireland (subject to compliance with the Companies Act). Where a company holds its annual general meeting or extraordinary general meeting outside of Ireland, the Companies Act requires that the company, at its own expense, make all necessary arrangements to ensure that members can by technological means participate in the meeting without leaving Ireland (unless all of the members entitled to attend and vote at the meeting consent in writing to the meeting being held outside of Ireland).

Notice of an annual general meeting must be given to all of the Company's shareholders and to its auditors. The Company's Constitution provides for a minimum notice period of 21 clear days, which is the minimum permitted under Irish law.

The only matters which must, as a matter of Irish law, be transacted at an annual general meeting are the presentation of the annual financial statements and reports of the directors and auditors, a review by the shareholders of the company's affairs, the appointment of new auditors and the fixing of the auditor's remuneration (or delegation of same). If no resolution is made in respect of the reappointment of an existing auditor at an annual general meeting, the existing auditor will be deemed to have continued in office.

Extraordinary General Meetings of Shareholders

Extraordinary general meetings may be convened by (i) the Company's board of directors, (ii) on requisition of the Company's shareholders holding not less than 10% of its paid up share capital carrying voting rights, (iii) on requisition of the Company's auditors or (iv) in exceptional cases, by order of the court. Extraordinary general meetings are generally held for the purpose of approving shareholder resolutions as may be required from time to time. At any extraordinary general meeting only such business shall be conducted as is set forth in the notice thereof.

Notice of an extraordinary general meeting must be given to all of the Company's shareholders and to its auditors. Under Irish law and the Company's Constitution, the minimum notice periods are 21 clear days' notice in writing for an extraordinary general meeting to approve a special resolution and 14 clear days' notice in writing for any other extraordinary general meeting.

In the case of an extraordinary general meeting convened by the Company's shareholders, the proposed purpose of the meeting must be set out in the requisition notice. Upon receipt of any such valid requisition notice, the Company's board of directors has 21 days to convene a meeting of its shareholders to vote on the matters set out

in the requisition notice. This meeting must be held within two months of the receipt of the requisition notice. If the Company's board of directors does not convene the meeting within such 21-day period, the requisitioning shareholders, or any of them representing more than one half of the total voting rights of all of them, may themselves convene a meeting, which meeting must be held within three months of the Company's receipt of the requisition notice.

If the Company's board of directors becomes aware that its net assets are not greater than half of the amount of the Company's called-up share capital, it must convene an extraordinary general meeting of its shareholders not later than 28 days from the date that they learn of this fact to consider how to address the situation.

Quorum for General Meetings

The Company's Constitution provides that no business shall be transacted at any general meeting unless a quorum is present. One or more of the Company's shareholders present in person or by proxy holding not less than a majority of the Company's issued and outstanding shares entitled to vote at the meeting in question constitute a quorum.

Voting

At general meetings of the Company, a resolution put to the vote of the meeting is decided on a poll. The Company's Constitution provides that its board of directors or its chairman may determine the manner in which the poll is to be taken and the manner in which the votes are to be counted.

Each shareholder is entitled to one vote for each ordinary share that he or she holds as of the record date for the meeting. Voting rights may be exercised by shareholders registered in the Company's share register as of the record date for the meeting or by a duly appointed proxy, which proxy need not be a shareholder. Where interests in shares are held by a nominee trust company, such company may exercise the rights of the beneficial holders on their behalf as their proxy. All proxies must be appointed in the manner prescribed by the Company's Constitution, which permits shareholders to notify the Company of their proxy appointments electronically in such manner as may be approved by the Company's board of directors.

In accordance with the Company's Constitution, it may from time to time be authorized by ordinary resolution to issue preferred shares. These preferred shares may have such voting rights as may be specified in the terms of such preferred shares (e.g., they may carry more votes per share than ordinary shares or may entitle their holders to a class vote on such matters as may be specified in the terms of the preferred shares). Treasury shares or the Company's shares that are held by its subsidiaries are not entitled to be voted at general meetings of shareholders.

Irish law requires special resolutions of the Company's shareholders at a general meeting to approve certain matters. Examples of matters requiring special resolutions include:

- amending the objects or memorandum of association of the Company;
- amending the articles of association of the Company;
- approving a change of name of the Company;
- authorizing the entering into of a guarantee or provision of security in connection with a loan, quasi- loan or credit transaction to a director or a person who is deemed to be "connected" to a director for the purposes of the Companies Act;
- opting out of preemption rights on the issuance of new shares;
- re-registration of the Company from a public limited company to a private company;
- variation of class rights attaching to classes of shares (where the articles of association do not provide otherwise);

- purchase of the Company's shares off market;
- reduction of issued share capital;
- sanctioning a compromise/scheme of arrangement with creditors or shareholders;
- resolving that the Company be wound up by the Irish courts;
- resolving in favor of a shareholders' voluntary winding-up; and
- setting the re-issue price of treasury shares.

Unanimous Shareholder Consent to Action Without Meeting

The Companies Act provides that shareholders may approve an ordinary or special resolution of shareholders without a meeting only if (i) all shareholders sign the written resolution and (ii) the company's articles of association permit written resolutions of shareholders (the Company's articles of association contain the appropriate authorizations for this purpose).

Variation of Rights Attaching to a Class or Series of Shares

Under the Company's Constitution and the Companies Act, any variation of class rights attaching to its issued shares must be approved by a special resolution of the Company's shareholders of the affected class or with the consent in writing of the holders of three-quarters of all the votes of that class of shares.

The provisions of the Company's Constitution relating to general meetings apply to general meetings of the holders of any class of the Company's shares except that the necessary quorum is determined in reference to the shares of the holders of the class. Accordingly, for general meetings of holders of a particular class of the Company's shares, a quorum consists of the holders present in person or by proxy representing at least one half of the issued shares of the class.

Inspection of Books and Records

Under Irish law, shareholders have the right to: (i) receive a copy of the Company's Constitution and any act of the Irish Government which alters its memorandum; (ii) inspect and obtain copies of the minutes of general meetings and the Company's resolutions; (iii) inspect and receive a copy of the register of shareholders, register of directors and secretaries, register of directors' interests and other statutory registers maintained in respect of the ordinary shares; (iv) receive copies of financial statements and directors' and auditors' reports which have previously been sent to shareholders prior to an annual general meeting; and (v) receive financial statements of any of the Company's subsidiaries that have previously been sent to shareholders prior to an annual general meeting for the preceding ten years. The Company's auditors also have the right to inspect all of the Company's books, records and vouchers. The auditors' report must be circulated to the shareholders with the Company's financial statements prepared in accordance with Irish law 21 clear days before the annual general meeting and must be read to the shareholders at the Company's annual general meeting.

Acquisitions

An Irish public limited company may be acquired in a number of ways, including:

- a court-approved scheme of arrangement under the Companies Act. A scheme of arrangement with shareholders requires a court order from the Irish High Court and the approval of a majority in number representing 75% in value of the shareholders present and voting in person or by proxy at a meeting called to approve the scheme;
- through a tender or takeover offer by a third party for all of the Company's shares. Where the holders of 80% or more of the Company's shares have accepted an offer for their shares, the remaining shareholders

may also be statutorily required to transfer their shares, and if the bidder does not exercise its "squeeze out" right, then the non-accepting shareholders also have a statutory right to require the bidder to acquire their shares on the same terms. If the Company's shares were to be listed on the main securities market of Euronext Dublin or another main securities market or regulated stock exchange in the European Union, this threshold would be increased to 90%; and

- by way of a merger with an EU-incorporated company under the EU Directive 2017/1132 relating to certain aspects of Company Law (as amended) and the European Communities (Cross-Border Mergers) Regulations 2008 (as amended). Such a merger must be approved by a special resolution.

Irish law does not generally require shareholder approval for a sale, lease or exchange of all or substantially all of a company's property and assets, unless the company is listed on a regulated stock exchange in the European Union.

Appraisal Rights

Generally, under Irish law, shareholders of an Irish company do not have dissenters' or appraisal rights. Under the European Communities (Cross-Border Mergers) Regulations 2008 governing the merger of an Irish company limited by shares such as the Company and a company incorporated in the European Economic Area (the European Economic Area includes all member states of the European Union and Norway, Iceland and Liechtenstein), a shareholder (i) who voted against the special resolution approving the merger or (ii) of a company in which 90% of the shares are held by the other party to the merger, has the right to request that the company acquire its shares for cash at a price determined in accordance with the share exchange ratio set out in the merger agreement.

Disclosure of Interests in Shares

Under the Companies Act, subject to certain limited exceptions, a person must notify the Company (but not the public) if, as a result of a transaction, such person will become interested in three percent or more of the Company's voting shares, or if as a result of a transaction a shareholder who was interested in more than three percent of its voting shares ceases to be so interested. Where any person is interested in more than three percent of the Company's voting shares, such person must notify the Company of any alteration of his or her interest that brings his or her total holding through the nearest whole percentage number, whether an increase or a reduction. The relevant percentage figure is calculated by reference to the aggregate nominal value of the voting shares in which the person is interested as a proportion of the entire nominal value of the Company's issued share capital (or any such class of share capital in issue). Where the percentage level of the person's interest does not amount to a whole percentage, this figure may be rounded down to the next whole number. The Company must be notified within five business days of the transaction or alteration of the person's interests that gave rise to the notification requirement. If a person fails to comply with these notification requirements, such person's rights in respect of any of the Company's shares he or she holds will not be enforceable, either directly or indirectly. However, such person may apply to the court to have the rights attaching to such shares reinstated.

In addition to these disclosure requirements, the Company, under the Companies Act, may, by notice in writing, require a person whom the Company knows or has reasonable cause to believe to be, or at any time during the three years immediately preceding the date on which such notice is issued to have been, interested in shares comprised in the Company's relevant share capital to: (i) indicate whether or not it is the case; and (ii) where such person holds or has during that time held an interest in the Company's shares, to provide additional information, including the person's own past or present interests in the Company's shares. If the recipient of the notice fails to respond within the reasonable time period specified in the notice, the Company may apply to a court for an order directing that the affected shares be subject to certain restrictions, as prescribed by the Companies Act, as follows:

- any transfer of those shares or, in the case of unissued shares, any transfer of the right to be issued with shares and any issue of shares, shall be void;

- no voting rights shall be exercisable in respect of those shares;
- no further shares shall be issued in right of those shares or in pursuance of any offer made to the holder of those shares; and
- no payment shall be made of any sums due from the Company on those shares, whether in respect of capital or otherwise.

The court may also order that shares subject to any of these restrictions be sold with the restrictions terminating upon the completion of the sale.

In the event the Company is in an offer period pursuant to the Irish takeover rules, as defined below, accelerated disclosure provisions apply for persons holding an interest in the Company's securities of one percent or more.

Anti-Takeover Provisions

Irish Takeover Rules and Substantial Acquisition Rules

A transaction in which a third party seeks to acquire 30% or more of the voting rights of the Company and certain other acquisitions of the Company's securities are governed by the Irish Takeover Panel Act 1997 and the Irish Takeover Rules made thereunder, which are referred to herein as the "Irish takeover rules," and are regulated by the Irish Takeover Panel. The "General Principles" of the Irish takeover rules and certain important aspects of the Irish takeover rules are described below.

General Principles

The Irish takeover rules are built on the following General Principles which will apply to any transaction regulated by the Irish Takeover Panel:

- in the event of an offer, all holders of securities of the target company must be afforded equivalent treatment and, if a person acquires control of a company, the other holders of securities must be protected;
- the holders of securities in the target company must have sufficient time and information to enable them to reach a properly informed decision on the offer; where it advises the holders of securities, the board of directors of the target company must give its views on the effects of the implementation of the offer on employment, employment conditions and the locations of the target company's place of business;
- a target company's board of directors must act in the interests of the company as a whole and must not deny the holders of securities the opportunity to decide on the merits of the offer;
- false markets must not be created in the securities of the target company, the bidder or any other company concerned by the offer in such a way that the rise or fall of the prices of the securities becomes artificial and the normal functioning of the markets is distorted;
- a bidder can only announce an offer after ensuring that he or she can pay in full the consideration offered, if such is offered, and after taking all reasonable measures to secure the implementation of any other type of consideration;
- a target company may not be hindered in the conduct of its affairs longer than is reasonable by an offer for its securities (this is a recognition that an offer will disrupt the day-to-day running of a target company, particularly if the offer is hostile and the board of directors of the target company must direct its attention to resisting the offer); and
- an acquisition of securities (whether such acquisition is to be effected by one transaction or a series of transactions) shall take place only at an acceptable speed and shall be subject to adequate and timely disclosure. Specifically, the acquisition of 10% or more of the issued voting shares within a seven day

period that would take a shareholder's holding to or above 15% of the issued voting shares (but less than 30%) is prohibited, subject to certain exemptions.

Mandatory Bid

Under certain circumstances, a person who acquires ordinary shares, or other of the Company's voting securities, may be required under the Irish takeover rules to make a mandatory cash offer for the remaining issued and outstanding voting securities at a price not less than the highest price paid for the securities by the acquiror, or any parties acting in concert with the acquiror, during the previous 12 months. This mandatory bid requirement is triggered if an acquisition of securities would increase the aggregate holding of an acquiror, including the holdings of any parties acting in concert with the acquiror, to securities representing 30% or more of the voting rights in the Company, unless the Irish Takeover Panel otherwise consents. An acquisition of securities by a person holding, together with its concert parties, securities representing between 30% and 50% of the voting rights in the Company would also trigger the mandatory bid requirement if, after giving effect to the acquisition, the percentage of the voting rights held by that person (together with its concert parties) would increase by 0.05% within a 12-month period. Any person (excluding any parties acting in concert with the holder) holding securities representing more than 50% of the voting rights of a company is not subject to these mandatory offer requirements in purchasing additional securities.

Voluntary bid; Requirements to Make a Cash Offer and Minimum Price Requirements

If a person makes a voluntary offer to acquire the issued and outstanding ordinary shares of the Company and the bidder acquired ordinary shares in the three-month period prior to the commencement of the offer period, the offer price must not be less than the highest price paid for ordinary shares by the bidder or its concert parties during that period. The Irish Takeover Panel has the power to extend the "look back" period to 12 months if the Irish Takeover Panel, taking into account the General Principles, believes it is appropriate to do so.

If the bidder or any of its concert parties has acquired more than 10% of the issued and outstanding ordinary shares (i) during the period of 12 months prior to the commencement of the offer period or (ii) at any time after the commencement of the offer period, the offer must be in cash (or accompanied by a full cash alternative) and the price per ordinary share must not be less than the highest price paid by the bidder or its concert parties during, in the case of (i), the 12-month period prior to the commencement of the offer period or, in the case of (ii), the offer period. The Irish Takeover Panel may apply this rule to a bidder who, together with its concert parties, has acquired less than 10% of the total ordinary shares in the 12-month period prior to the commencement of the offer period if the Irish Takeover Panel, taking into account the General Principles, considers it just and proper to do so.

An offer period will generally commence on the date of the first announcement of the offer or proposed offer.

Substantial Acquisition Rules

The Irish takeover rules also contain rules governing substantial acquisitions of shares and other voting securities which restrict the speed at which a person may increase his or her holding of shares and rights over shares to an aggregate of between 15% and 30% of the voting rights of the Company. Except in certain circumstances, an acquisition or series of acquisitions of shares or rights over shares representing 10% or more of the voting rights of the Company is prohibited, if such acquisition(s), when aggregated with shares or rights already held, would result in the acquirer holding 15% or more but less than 30% of the voting rights of the Company and such acquisitions are made within a period of seven days. These rules also require accelerated disclosure of acquisitions of shares or rights over shares relating to such holdings.

Frustrating Action

Under the Irish takeover rules, the Company's board of directors is not permitted to take any action that might frustrate an offer for its shares once the Company's board of directors has received an approach that may lead to an

offer or has reason to believe that such an offer is or may be imminent, subject to certain exceptions. Potentially frustrating actions such as (i) the issue of shares, options or convertible securities, (ii) material acquisitions or disposals, (iii) entering into contracts other than in the ordinary course of business or (iv) any action, other than seeking alternative offers, which may result in frustration of an offer, are prohibited during the course of an offer or at any earlier time during which the Company's board of directors has reason to believe an offer is or may be imminent. Exceptions to this prohibition are available where:

- the action is approved by the Company's shareholders at a general meeting; or
- the Irish Takeover Panel has given its consent, where:
- it is satisfied the action would not constitute frustrating action;
- the Company's shareholders holding more than 50% of the voting rights state in writing that they approve the proposed action and would vote in favor of it at a general meeting;
- the action is taken in accordance with a contract entered into prior to the announcement of the offer (or any earlier time at which the Company's board of directors considered the offer to be imminent); or
- the decision to take such action was made before the announcement of the offer and either has been at least partially implemented or is in the ordinary course of business.

Other Provisions

Certain other provisions of Irish law or the Company's Constitution may be considered to have anti-takeover effects, including advance notice requirements for director nominations and other shareholder proposals, as well those described under the following captions: "*—Capital Structure—Authorized Share Capital*" (regarding issuance of preferred shares), "*—Preemption Rights, Share Warrants and Share Options*," "*—Disclosure of Interests in Shares*" and "*—Corporate Governance*."

Corporate Governance

The Company's Constitution delegates the day-to-day management of the Company to the board of directors. The Company's board of directors may then delegate the management of the Company to committees of the board of directors (consisting of one or more members of the board of directors) or executives; regardless, the Company's board of directors remains responsible, as a matter of Irish law, for the proper management of the affairs of the company. Committees may meet and adjourn as they determine proper. A vote at any committee meeting will be determined by a majority of votes of the members present.

The Company's board of directors has a standing audit committee, a compensation committee and a nominating and corporate governance committee, with each committee comprised solely of independent directors, as prescribed by The NASDAQ Global Select Market listing standards and SEC rules and regulations. The Company has adopted corporate governance policies, including a code of conduct and an insider trading policy, as well as an open door reporting policy and a comprehensive compliance program.

The Companies Act require a minimum of two directors. The Company's Constitution provides that the board may determine the size of the board from time to time.

The Company's board of directors is divided into three classes, designated Class I, Class II and Class III. The term of the Class I directors will expire on the date of the 2024 annual general meeting; the term of the Class II directors will expire on the date of the 2022 annual general meeting; and the term of the Class III directors will expire on the date of the 2023 annual general meeting. At each annual general meeting of shareholders, successors to the class of directors whose term expires at that annual general meeting are elected for a three-year term. In no case will any decrease in the number of directors shorten the term of any incumbent director. A director may hold office until the annual general meeting of the year in which his or her term expires and until his or her successor is

elected and duly qualified, subject to his or her prior death, resignation, retirement, disqualification or removal from office.

Directors are elected by ordinary resolution at a general meeting. Irish law requires majority voting for the election of directors, which could result in the number of directors falling below the prescribed minimum number of directors due to the failure of nominees to be elected. Accordingly, the Company's Constitution provides that if, at any general meeting of shareholders, the number of directors is reduced below the minimum prescribed by the Constitution due to the failure of any person nominated to be a director to be elected, then, in such circumstances, the nominee or nominees who receive the highest number of votes in favor of election will be elected in order to maintain such prescribed minimum number of directors. Each director elected in this manner will remain a director (subject to the provisions of the Companies Act and the articles of association) only until the conclusion of the next annual general meeting unless he or she is reelected.

Under the Companies Act and notwithstanding anything contained in the Constitution or in any agreement between the Company and a director, the Company's shareholders may, by an ordinary resolution, remove a director from office before the expiration of his or her term at a meeting held on no less than 28 days' notice and at which the director is entitled to be heard. The power of removal is without prejudice to any claim for damages for breach of contract (e.g. employment contract) that the director may have against the Company in respect of his removal.

The Company's Constitution provides that the board of directors may fill any vacancy occurring on the board of directors. If the Company's board of directors fills a vacancy, the director's term expires at the next annual general meeting. A vacancy on the board of directors created by the removal of a director may be filled by the shareholders at the meeting at which such director is removed and, in the absence of such election or appointment, the remaining directors may fill the vacancy.

Legal Name; Formation; Fiscal Year; Registered Office

Jazz Pharmaceuticals Public Limited Company is the Company's current legal and commercial name. The Company was incorporated in Ireland on March 15, 2005 as a private limited company (registration number 399192) under the name Azur Pharma Limited. Azur Pharma Limited was re-registered as a public limited company named Azur Pharma Public Limited Company effective October 20, 2011, and was subsequently renamed Jazz Pharmaceuticals Public Limited Company on January 16, 2012. The Company's fiscal year ends on December 31st and its registered address is Fifth Floor, Waterloo Exchange, Waterloo Road, Dublin 4, Ireland D04 E5W7.

Duration; Dissolution; Rights Upon Liquidation

The Company's duration is unlimited. The Company may be dissolved and wound up at any time by way of a shareholders' voluntary winding up or a creditors' winding up. In the case of a shareholders' voluntary winding up, a special resolution of shareholders is required. The Company may also be dissolved by way of court order on the application of a creditor, or by the Companies Registration Office as an enforcement measure where it has failed to file certain returns.

The Company's Constitution provides that the ordinary shareholders are entitled to participate pro rata in a winding up, but their right to do so may be subject to the rights of any preferred shareholders to participate under the terms of any series or class of preferred shares.

Certificated Shares

Pursuant to the Companies Act, a shareholder is entitled to be issued a share certificate on request and subject to payment of a nominal fee.

No Sinking Fund

Ordinary shares have no sinking fund provisions.

Stock Exchange Listing

Ordinary shares are listed on The NASDAQ Global Select Market under the trading symbol “JAZZ.” Ordinary shares are not currently intended to be listed on the Irish Stock Exchange.

Transfer and Registration of Shares

The transfer agent and registrar for ordinary shares is Computershare Trust Company, N.A. Its address is 250 Royall Street, Canton, MA 02021. An affiliate of the transfer agent maintains the share register, registration in which is determinative of ownership of ordinary shares. A shareholder who holds shares beneficially is not the holder of record of such shares. Instead, the depository (for example, Cede & Co., as nominee for DTC) or other nominee is the holder of record of those shares. Accordingly, a transfer of shares from a person who holds such shares beneficially to a person who also holds such shares beneficially through a depository or other nominee will not be registered in the Company’s official share register, as the depository or other nominee will remain the record holder of any such shares.

A written instrument of transfer is required under Irish law in order to register on the Company’s official share register any transfer of shares (i) from a person who holds such shares directly to any other person, (ii) from a person who holds such shares beneficially but not directly to a person who holds such shares directly, or (iii) from a person who holds such shares beneficially to another person who holds such shares beneficially where the transfer involves a change in the depository or other nominee that is the record owner of the transferred shares. An instrument of transfer is also required for a shareholder who directly holds shares to transfer those shares into his or her own broker account (or vice versa). Such instruments of transfer may give rise to Irish stamp duty, which must be paid prior to registration of the transfer on the Company’s official Irish share register. However, a shareholder who directly holds shares may transfer those shares into his or her own broker account (or vice versa) without giving rise to Irish stamp duty provided there is no change in the ultimate beneficial ownership of the shares as a result of the transfer and the transfer is not made in contemplation of a sale of the shares.

Any transfer of ordinary shares that is subject to Irish stamp duty will not be registered in the name of the buyer unless an instrument of transfer is duly stamped and provided to the transfer agent. The Company, in its absolute discretion and insofar as the Companies Act or any other applicable law permit, may, or may provide that any of its subsidiaries will, pay Irish stamp duty arising on a transfer of ordinary shares on behalf of the transferee of such ordinary shares. If stamp duty resulting from the transfer of ordinary shares which would otherwise be payable by the transferee is paid by the Company or any of its subsidiaries on behalf of the transferee, then in those circumstances, the Company will, on its behalf or on behalf of its subsidiary (as the case may be), be entitled to (i) seek reimbursement of the stamp duty from the transferee, (ii) set-off the stamp duty against any dividends payable to the transferee of those ordinary shares and (iii) to claim a first and permanent lien on ordinary shares on which stamp duty has been paid by the Company or its subsidiary for the amount of stamp duty paid. The Company’s lien shall extend to all dividends paid on those ordinary shares. Parties to a share transfer may assume that any stamp duty arising in respect of a transaction in ordinary shares has been paid unless one or both of such parties is otherwise notified.

The Company’s Constitution delegates to the secretary or assistant secretary of the Company the authority, on behalf of the Company, to execute an instrument of transfer on behalf of a transferring party. Under the Company’s Constitution, the directors can also authorize any person to execute an instrument of transfer on behalf of a transferring party in certain circumstances.

In order to help ensure that the official share register is regularly updated to reflect trading of ordinary shares occurring through normal electronic systems, the Company intends to regularly produce any required instruments of

transfer in connection with any transactions for which stamp duty is paid (subject to the reimbursement and set-off rights described above). In the event that the Company notifies one or both of the parties to a share transfer that its believes stamp duty is required to be paid in connection with the transfer and that the Company will not pay the stamp duty, the parties may either themselves arrange for the execution of the required instrument of transfer (and may request a form of instrument of transfer from the Company for this purpose) or request that the Company execute an instrument of transfer on behalf of the transferring party. In either event, if the parties to the share transfer have the instrument of transfer duly stamped (to the extent required) and then provide it to the Company's transfer agent, the buyer will be registered as the legal owner of the relevant shares on the Company's official Irish share register (subject to the suspension right described below).

The directors may suspend registration of transfers from time to time, not exceeding 30 days in aggregate each year.

Irish Restrictions on Import and Export of Capital

Except as indicated below, there are no restrictions on non-residents of Ireland dealing in Irish domestic securities, which includes ordinary shares of Irish companies. Except as indicated below, dividends and redemption proceeds also continue to be freely transferable to non-resident holders of such securities.

The Financial Transfers Act, 1992, provides that the Irish Minister for Finance can make provision for the restriction of financial transfers between Ireland and other countries. For the purposes of this Act, "financial transfers" include all transfers which would be movements of capital or payments within the meaning of the treaties governing the European Communities if they had been made between Member States of the Communities. This Act has been used by the Minister for Finance to implement European Council Directives, which provide for the restriction of financial transfers to certain countries, organizations and people including the Al-Qaeda network and the Taliban, Afghanistan, Belarus, Democratic People's Republic of Korea, Democratic Republic of Congo, Iran, Iraq, Ivory Coast, Lebanon, Liberia, Libya, Republic of Guinea, Somalia, Sudan, Syria Tunisia, Ukraine and Zimbabwe.

Any transfer of, or payment in respect of, a share or interest in a share involving the government of any country that is currently the subject of United Nations sanctions, any person or body controlled by any of the foregoing, or by any person acting on behalf of the foregoing, may be subject to restrictions pursuant to such sanctions as implemented into Irish law.

Amendment Three to Pharmacy Master Services Agreement

This Amendment Three to the Pharmacy Master Services Agreement dated July 1, 2020 (this "Amendment") is by and between Jazz Pharmaceuticals, Inc. and Express Scripts Specialty Distribution Services, Inc. ("ESSDS") (collectively, the "Parties") and is entered into by and between the Parties as of December 7, 2021 (the "Effective Date").

WHEREAS, the Parties entered into a Pharmacy Master Services Agreement effective as of July 1, 2020 (the "Agreement");

WHEREAS, the Parties desire to amend the Agreement as set forth herein with the intent of ensuring Adverse Events and Product Complaints for all Product Marketed by Jazz and reported to ESSDS in connection with their services under the Agreement are collected and reported to Jazz;

NOW, THEREFORE, in consideration of the promises, mutual covenants, representations, and warranties set forth herein, the Parties agree as follows:

1. Section 1.25 shall be amended and restated to read as follows:

   1.25 "Products" shall mean Xyrem® (sodium oxybate) oral solution and dosing kit, and Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution.

2. Section 1.26 shall be amended and restated to read as follows:

   1.26 "Product Complaint" shall mean notification relating to quality, purity, identity, potency, packaging, tampering, and/or quality aspect of the Products, or any Products Marketed by Jazz.

3. A new section 1.26a shall be added to read as follows:

   1.26a "Products Marketed by Jazz" shall mean any medicine other than the Products as defined in Section 1.25, which are marketed by Jazz Pharmaceuticals in the U.S., including Sunosi™ (solriamfetol), Epidiolex® (cannabidiol), Defitelio® (defibrotide sodium), Rylaze™ asparaginase erwinia chrysanthemi (recombinant)-rywn, Vyxeos® (daunorubicin and cytarabine), and Zepzelca (lurbinectedin). The list of Products Marketed by Jazzmay be amended from time to time upon written notice to ESSDS, and any such amendments to the list will be incorporated into the applicable mutually agreed upon SOPs and Work Instructions.

4. A new section 7.3a shall be added to read as follows:

   7.3a <u>Adverse Event and Product Compliant Reporting for Products Marketed by Jazz.</u> All Adverse Events and Product Complaints for Products Marketed by Jazz that are reported to ESSDS in connection with services provided by ESSDS under the

Agreement will be collected and reported to Jazz pursuant to the terms of this agreement and any relevant Work Order, Work Instructions and/or SOPs;

5. Except as specifically modified herein, all other terms and conditions of the Agreement shall remain in full force and effect.

IN WITNESS WHEREOF, the Parties have caused this Amendment to be executed by their duly authorized representatives as of the Effective Date.

AGREED TO:	**AGREED TO:**
Jazz Pharmaceuticals, Inc.	**Express Scripts Specialty Distribution Services, Inc.**
Signature: /s/ Debra Feldman	Signature: Joshua Parker
Name: Debra S. Feldman	Name; Joshua Parker
Title: VP, Global Pharmacovigilance & Labeling	Title: VP
Date: 22-Dec-2021	Date: 12/07/2021 | 1:16 PM CST

RPM for JLD 12.7.21

JAZZ PHARMACEUTICALS
GLOBAL CASH BONUS PLAN

1. Purpose of the Plan.

The Jazz Pharmaceuticals Global Cash Bonus Plan (the "***Plan***") is designed to provide meaningful incentive, on an annual basis, for employees of Jazz Pharmaceuticals plc (the "***Company***") and employees of the Company's Affiliates.

2. Eligibility.

In order to be eligible to participate in the Plan for a Plan Year, an employee (a) must be an employee of the Company or an Affiliate whose Employment Start Date is 31 October of the Plan Year or earlier within the Plan Year, (b) must not be eligible to participate in a commercial (including sales) or other similar incentive compensation plan, and (c) must not be eligible to receive separate annual bonus compensation under an employment-related contract or another annual bonus program, as determined by the Company or an Affiliate. Additionally, with respect to Gentium S.r.l., Jazz Pharmaceuticals Italy S.r.l. and any other Specified Affiliate in Italy (other than Jazz Healthcare Italy S.r.l.), only employees who are classified as "dirigenti" under Italian employment laws and are individually notified in a separate writing of their eligibility to participate in the Plan. Unless otherwise expressly and individually designated as a Participant by the Company or an Affiliate in writing, employees who are employed under a temporary contract or as interns are not eligible to be Participants, to the extent permissible under applicable local law.

In order to be eligible to receive a Bonus for a Plan Year, a Participant must (i) continue to be an employee of the Company or an Affiliate in good standing, as determined at the discretion of the particular Affiliate which is the Participant's employer (the "***Employer***"), from the date his/her participation in the Plan commences for the Plan Year until the Bonus Payment Date (as defined in Section 7) for the Plan Year, except as provided in Section 6, (ii) act in accordance with the Company's Code of Conduct, compliance policies and procedures, and those of the Employer, and applicable laws and regulations during the Plan Year, and (iii) not be serving a termination notice period as of the Bonus Payment Date for the Plan Year.

3. Target Bonus.

The Target Bonus for Participants who are not Section 16 officers of the Company is determined within the discretion of the Chief Executive Officer, and the Target Bonus may vary from year to year and between positions, and among positions at the same level. No Participant has any contractual or otherwise acquired rights to a Target Bonus pursuant to any previous target bonus (whether set forth in a written plan or otherwise). Participants in Italy who are classified as "dirigenti" under Italian employment laws will be provided written notice specifying such Participant's Target Bonus.
As additional general guidelines, if a Participant moves to a position and/or responsibility level with a higher Target Bonus during a Plan Year, the Participant's Target Bonus will be reset at such higher level for the entire Plan Year; and if a Participant moves to a position and/or responsibility level with a lower Target Bonus during a Plan Year, the Participant's Target Bonus will be reset at the lower level for the entire Plan Year, to the extent permissible under applicable local law.

Notwithstanding the foregoing, for any Participant who is a Section 16 officer of Jazz Pharmaceuticals plc, the Board or the Compensation and Management Development Committee ("***Committee***") will determine such Participant's Target Bonus for each Plan Year.

4. Bonus Pool and Bonuses.

Following the end of a Plan Year, the Board or the Committee will determine, in its sole discretion, the Bonus Pool for the Plan Year to be allocated for the payment of Bonuses to Participants. The Bonus Pool will be calculated by multiplying

(a) the sum of the following amounts for each Participant:

(i) the Base Salary for such Participant, multiplied by

(ii) such Participant's applicable Target Bonus;
with

(b) the percentage set by the Board or the Committee based upon its determination of the Company's success in achieving the objectives established by the Board or the Committee for funding the Bonus Pool for the Plan Year (the "***Bonus Pool Objectives***").

The Bonus Pool Objectives are related to the achievement of the overall corporate objectives established for the applicable Plan Year by the Board or the Committee (the "***Corporate Objectives***").

At the discretion of the Board or the Committee, the Bonus Pool will be reduced by the amount of bonuses that are required to be paid to any Participants under applicable collective bargaining agreements, labor union arrangements, or the like, if any.

Except as provided in Section 5, a Participant's Bonus (on a gross basis) for a Plan Year will be based upon the following criteria, as determined within the discretion of the Board, the Committee, or the Company's or Employer's management: (a) the Company's success in achieving the Corporate Objectives established for the Plan Year, (b) the Participant's success in achieving his/her individual objectives established for the Plan Year (if applicable) and the Participant's contribution to the Company's success in achieving the Corporate Objectives, in each case while demonstrating Company values, and (c) the Participant's compliance with Company policies and those of the Employer as evaluated at the discretion of the Employer. Applying these criteria, a Participant may (or may not) be entitled to any Bonus. A Participant's Bonus, if any, will be reduced by the amount of any bonuses that are required to be paid to the Participant under applicable collective bargaining agreements, labor union arrangements, or the like, to the extent applicable. Each Participant's Bonus for a Plan Year will be approved by the Chief Executive Officer or his/her delegate, except that in the case of any Participant who is a Section 16 Officer of Jazz Pharmaceuticals plc, such Participant's Bonus will be approved by the Board or the Committee.

The maximum Bonus payable to any Participant with respect to a Plan Year is 300% of the Participant's Target Bonus.

The total of all Bonuses paid under this Plan in any Plan Year may not exceed the Bonus Pool for such Plan Year unless such excess amount is specifically approved by the Board or the Committee. Except as provided in Section 5, no amounts will be payable to any Participant hereunder until the Bonus Pool and such Participant's Bonus have been determined as described above. Except as provided in Section 5, no Participant is entitled to any particular bonus, or any bonus, unless approved as described above.

5. Termination of Employment; Death; Retirement; Permanent Disability.

No Bonus, prorated or otherwise, will be paid to any Participant whose employment with the Company or an Affiliate terminates prior to the Bonus Payment Date, except as set forth in this Section 5 or if otherwise required under applicable regulations or laws.

If a Participant's employment terminates due to the Participant's death or Permanent Disability at any time during the Plan Year, the Participant (or their beneficiary, if the Participant is deceased) will be eligible to receive a prorated Bonus calculated based on the termination date (if within the Plan Year), or full year Bonus if termination occurs after the end of the Bonus Year but prior to the Bonus Payment Date. Such Bonus amount will be determined based on the applicable Target Bonus amount.

If a Participant's employment terminates due to the Participant's Retirement on or after July 1 in the Plan Year, and the Participant satisfies the Retirement Bonus Conditions (discussed below), the Participant (or their beneficiary, if the Participant is deceased) will be eligible to receive a prorated Bonus calculated based on the termination date (if within the Plan Year), or full year Bonus if termination occurs after the end of the Bonus Year but prior to the Bonus Payment Date. Such Bonus amount will be determined based on the applicable Target Bonus amount. The "***Retirement Bonus Conditions***" are as follows: (1) the Participant must provide their Employer at least four (4) months of advance written notice of intention to terminate their employment, and (2) the Participant must execute and deliver a non-solicitation agreement satisfactory to their Employer that will apply for a period of twelve (12) months after their employment termination date.

Any Bonuses paid pursuant to this Section 5 may be paid at the time determined by the Company's or Employer's management, which will in no event be later than the Bonus Payment Date for the applicable Plan Year.

Unless otherwise required under applicable local law, payments under this Plan shall not be included in calculation of any payment in lieu of notice, severance pay, redundancy pay, termination, indemnity or similar pay.

6. Payment of Bonuses.

Bonuses for a Plan Year will be paid in cash to a Participant (or his/her beneficiary, in the event of death) by 15 March of the following year (the "***Bonus Payment Date***"), except (i) as is otherwise determined in the sole discretion of the Board, the Committee or the Company's management, as appropriate, or (ii) as may be necessary or advisable to comply with regulations, laws, employment agreements or employment contracts applicable to a particular Participant.

Notwithstanding the foregoing, in all cases, the payment date of any Bonus for any Participant who is subject to Section 409A of the United States Internal Revenue Code of 1986, as amended, or any state law of similar effect ("***Section 409A***") will be designed to either comply with Section 409A or satisfy an exemption from application of Section 409A, and the Plan will be administered and interpreted to the greatest extent possible in compliance with Section 409A or in accordance with such exemption, as applicable. Benefits under this Plan are not transferable, to the extent permissible under applicable local law, and the Plan is unfunded.

7. Withholding of Taxes and Mandatory Contributions.

Bonuses will be subject to applicable tax and social security withholding as required by applicable local laws, including but not limited to income and employment taxes.

8. Plan Amendments.

This Plan may be revised, modified, or terminated at any time in the sole discretion of: (a) the Board; (b) the Committee; and (c) by the Chief Executive Officer to the extent such revisions or modifications do not impact any Section 16 officers of the Company. Without limiting the foregoing, the Plan may be revised, modified, or terminated with respect to a Participant or specific group of Participants as may be necessary or advisable to comply with the laws and regulations of the jurisdiction where such Participant or specific group of Participants are employed or where such Participant or specific group of Participants are tax residents.

9. No Employment Rights; No Acquired Rights.

Nothing contained in this Plan is intended to confer any right upon any employee to continued employment with the Employer, Company or any Affiliates.

Any payment of Bonuses would be on a voluntary and discretionary basis, without creating any contractual or other acquired right to participate with respect to a similar (or any other) bonus plan or to receive any similar awards (or benefits in lieu) in the future.

10. Plan Administration.

This Plan will be administered by the Board or the Committee. The Board and the Committee shall have the sole discretion and authority to administer and interpret the Plan, and the decisions of the Board and the Committee shall in every case be final and binding on all persons having an interest in the Plan. Notwithstanding the foregoing, certain aspects of the Plan may be administered by the Chief Executive Officer or the Company's management (including but not limited to the Chief Human Resources Officer ("***CHRO***")), as specifically provided in the Plan, and in such event, the Chief Executive Officer or the Company's management (including the CHRO) shall have the sole discretion and authority to administer and interpret such aspects of the Plan, and the decisions of the Chief Executive Officer or the Company's management (including the CHRO) shall in such cases be final and binding.

11. Definitions.

"***Affiliate***" means any "parent" or "subsidiary" of the Company as such terms are defined in Rule 405 promulgated under the Securities Act and any "holding company" or "subsidiary" of the Company as such terms are defined in Section 8 and 7 respectively of the Companies Act. The Board shall have the authority to determine the time or times at which "parent" or "subsidiary" status is determined within the foregoing definition.

"***Base Salary***" for a Participant means the total amount of base salary or base pay actually paid to the Participant by the Employer during the period of his/her participation in the Plan for the Plan Year, rather than the Participant's base salary level or base pay level at any particular point during the Plan Year (*e.g.*, the Base Salary for a Participant whose base salary or base pay is adjusted during the Plan Year, for a Participant who is hired during the Plan Year, or for a Participant whose employment terminates during the Plan Year will be the total amount of base salary or base pay actually paid to the Participant during the period of his/her participation in the Plan for the Plan Year). Base Salary does not include any benefits, allowances, expense reimbursements, relocation payments or benefits, incentive compensation or bonuses, amounts

received as a result of equity awards, overtime or shift differential payments or similar one-time, extraordinary or unusual payments. Any salary or pay earned for periods during which a Participant is on disciplinary action or serving a termination notice period are excluded from Base Salary to the extent permissible under applicable local law and as determined within the discretion of the Company's or Employer's management.

"***Board***" means the Board of Directors of Jazz Pharmaceuticals plc.

"***Bonus***" means a Participant's actual bonus for a Plan Year as determined in accordance with Section 4 or Section 5, if applicable.

"***Bonus Pool***" for a Plan Year means the aggregate dollar amount set by the Board or the Committee for the payment of Bonuses for such Plan Year to Participants as set forth in Section 4.

"***Chief Executive Officer***" means the Chief Executive Officer of Jazz Pharmaceuticals plc.

"***Employment Start Date***" means the first business day on which a Participant is an employee of the Company or an Affiliate, on the Company's or such Affiliate's payroll, as applicable.

"***Participant***" means an employee of the Company or an Affiliate who meets all of the eligibility requirements set forth in Section 2.

"***Permanent Disability***" means that a Participant has become permanently disabled under any policy or program of disability income insurance then in force covering such Participant or, if none is in force, under applicable laws or regulations.

"***Plan***" means this Jazz Pharmaceuticals Global Cash Bonus Plan.

"***Plan Year***" means each calendar year beginning 1 January and ending 31 December.

"***Retirement***" means the Participant's voluntary termination of employment from their Employer (with no subsequent employment by the Company or any Affiliate), unless circumstances exist at the time of such termination that would constitute "cause" for termination (as defined in the Participant's employment contract, or if there is no such definition in the employment contract, under applicable laws), following: (a) the Participant's completion of five (5) years of continuous service as an employee with the Employer, the Company, or any other Affiliate, and (b) attainment of age 55.

"***Section 16 Officer***" means an individual who has been designated by the Board as an "officer" of Jazz Pharmaceuticals plc for the purposes of Section 16 of the Securities Exchange Act of 1934, as amended, and Rule 16a-1(f) thereunder.

"***Target Bonus***" means, for a Participant for a Plan Year, the percentage of Base Salary that represents the target amount of Bonus that such Participant may receive for the applicable Plan Year, as may be adjusted with respect to such Participant for such Plan Year in the discretion of the Board, the Committee or the Chief Executive Officer or his/her delegate, as applicable.

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As approved by the Compensation and Management Development Committee of the Board of Directors of Jazz Pharmaceuticals plc on 3 November 2021.

Exhibit 21.1

Subsidiaries of the Registrant

Name	State/Jurisdiction of Incorporation
Jazz Pharmaceuticals Ireland Limited	Ireland
Jazz Pharmaceuticals, Inc.	Delaware
Celator Pharmaceuticals Inc.	Delaware
GW Research Limited	United Kingdom
Jazz Financing I DAC	Ireland
Jazz Pharmaceuticals UK Holdings Limited	United Kingdom
Gentium S.r.l.	Italy
GW Pharma Limited	United Kingdom
Jazz Securities DAC	Ireland
Jazz Financing Holdings Limited	Ireland
Jazz Financing Lux S.à.r.l	Luxembourg
Jazz Pharmaceuticals International Limited	Bermuda
Jazz Investments Europe Limited	Malta
Jazz Investments I Limited	Bermuda
Jazz Capital Limited	Ireland
Jazz Pharmaceuticals UK Limited	United Kingdom
GW Pharmaceuticals Limited	United Kingdom

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the registration statements (No. 333-179075, No. 333-186886, No. 333-194131, No. 333-202269, No. 333-209767, No. 333-216338, No. 333-224757, No. 333-229889, No. 333-236636, No. 333-249807, No. 333-253417 and No. 333-255895) on Form S-8 of our reports dated March 1, 2022, with respect to the consolidated financial statements and financial statement schedule at Item 15(a)2 of Jazz Pharmaceuticals plc and the effectiveness of internal control over financial reporting.

/s/ KPMG

Dublin, Ireland
March 1, 2022

Exhibit 31.1

CERTIFICATION

I, Bruce C. Cozadd, certify that:

1. I have reviewed this Annual Report on Form 10-K of Jazz Pharmaceuticals public limited company;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 1, 2022

By: /s/ Bruce C. Cozadd

Bruce C. Cozadd
Chairman and Chief Executive Officer and Director

Exhibit 31.2

CERTIFICATION

I, Renée Galá, certify that:

1. I have reviewed this Annual Report on Form 10-K of Jazz Pharmaceuticals public limited company;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 1, 2022

By: /s/ Renée Galá

Renée Galá
Executive Vice President and Chief Financial Officer

Exhibit 32.1

CERTIFICATION[(1)]

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. Section 1350), Bruce C. Cozadd, Chief Executive Officer of Jazz Pharmaceuticals public limited company (the "Company"), and Renée Galá, Executive Vice President and Chief Financial Officer of the Company, each hereby certifies that, to the best of his knowledge:

1. The Company's Annual Report on Form 10-K for the year ended December 31, 2021, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Exchange Act; and

2. The information contained in the Periodic Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 1, 2022

/s/ Bruce C. Cozadd
Bruce C. Cozadd
Chairman and Chief Executive Officer and Director

/s/ Renée Galá
Renée Galá
Executive Vice President and Chief Financial Officer

(1) This certification accompanies the Annual Report on Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of Jazz Pharmaceuticals public limited company under the Securities Act of 1933, as amended, or the Exchange Act (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing. A signed original of this written statement required by Section 906 of the Sarbanes-Oxley Act of 2002 has been provided to Jazz Pharmaceuticals public limited company and will be retained by Jazz Pharmaceuticals public limited company and furnished to the Securities and Exchange Commission or its staff upon request.