


2021 Annual Report

GROWTH. REIMAGINED.

To **reimagine**
growth means
to envision it
— and then
cultivate it —
beyond just the
obvious places.

Horizon experienced tremendous growth in 2021, with record-breaking results. As a company, we also grew in many other ways that call for celebrating: namely in our global ambitions, our science, our employees and our role and reputation in the communities we serve.



**Like
everything
we do at
Horizon,
this growth
was powerful.
And it was
personal.**

Timothy P. Walbert
Chairman, President and
Chief Executive Officer



That starts with me.

Last fall, the company launched its first corporate awareness campaign, “For Us It’s Personal,” spotlighting my own experience as a patient living with both a rare disease and an autoimmune disease. The campaign will expand in 2022 with the stories of other Horizon colleagues — patients and caregivers just like me. As a biotechnology company, Horizon is able to make differences in the lives of patients not simply because of our groundbreaking therapies but because many of us are patients.

We recognize that in order to make progress in our industry, we must first see and understand the needs of patients — whether it’s those with observable diseases and symptoms or the “invisible” patients among us whose struggles often go undetected.

That is where true growth is happening today, and where it will continue as we constantly reimagine what we are capable of.

Here’s a look at some of our other spectacular areas of growth from 2021.

Business Growth

It bears repeating: 2021 was a record-breaking year for Horizon. Full-year 2021 net sales were \$3.23 billion, representing year-over-year growth of 47 percent, and our full-year 2021 adjusted EBITDA was \$1.28 billion, representing year-over-year growth of 33 percent.

Driving much of this growth was TEPEZZA®, which boasted one of the most successful rare disease medicine launches in history, and had full-year 2021 net sales of \$1.66 billion, representing year-over-year growth of 103 percent. This was a remarkable performance, given that TEPEZZA commercial supply was disrupted from late 2020 into April 2021 by the invocation of the Defense Production Act to allow drug manufacturers to focus on making COVID-19 vaccines. We executed a strong commercial relaunch following the supply resumption, getting patients on therapy quickly as Horizon continued to increase uptake of the medicine. We doubled our TEPEZZA commercial organization and we also added a second TEPEZZA drug manufacturer to provide additional capacity. Visibility grew as well, largely thanks to our first branded TEPEZZA television commercial in May, as well as our first celebrity-driven campaign featuring three-time Olympic gold medalist Gail Devers, who has dealt with Graves' disease

and symptoms of thyroid eye disease (TED) since the late 1980s.

TEPEZZA wasn't the only medicine driving exciting growth in our portfolio. KRYSTEXXA® saw full-year net 2021 sales of \$565.5 million, representing year-over-year growth of 39 percent. But the biggest news on the KRYSTEXXA front came in October with the release of top-line results of the MIRROR randomized control trial, which evaluated the use of KRYSTEXXA plus methotrexate, an immunomodulator commonly prescribed by rheumatologists. This study showed that 71 percent of patients on KRYSTEXXA plus methotrexate achieved a complete response compared to 39 percent of patients on KRYSTEXXA plus placebo. As a result, we submitted a supplemental biologics license application (sBLA) to the U.S. Food and Drug Administration in January 2022 seeking to expand the prescribing information for KRYSTEXXA to include methotrexate. Use of KRYSTEXXA plus immunomodulation is now approaching 50 percent of new patients.

UPLIZNA®, which became part of our portfolio with the acquisition of Viela Bio in March 2021, finished with full-year 2021 net sales of \$60.8 million after Horizon repositioned, rebranded and relaunched the medicine, all within six months. Horizon put



the right infrastructure in place; built a commercial team with deep neuroimmunology experience, relationships and market knowledge and bolstered our site-of-care and reimbursement support to support all aspects of the patient journey. The new commercial team connected with nearly 2,000 health care providers, and we broadly enhanced patient access as we invested in medical engagement to develop our scientific leadership position in neuromyelitis optica spectrum disorder (NMOSD).

In our rare disease business, RAVICTI®, PROCYSBI® and ACTIMMUNE® also performed well, driven by programs designed to help patients and their caregivers get answers to their common questions from physicians or others in similar situations. We also made significant strides to improve patient identification, compliance and adherence.

1. Adjusted EBITDA is a non-GAAP measure. Please refer to the discussion of non-GAAP financial measures and the reconciliations to GAAP measures in our Form 10-K for the year ended Dec. 31, 2021.

Except for five-year shareholder return, growth percentages represent comparison to full-year 2020. Total shareholder return through Dec. 31, 2021.

\$3.23B

2021 NET SALES

566%

5-YEAR TOTAL SHAREHOLDER RETURN

47%

NET SALES GROWTH OVER 2020

33%

ADJUSTED EBITDA GROWTH¹

TEPEZZA	\$ 1,661.3M
KRYSTEXXA	\$ 565.5M
RAVICTI	\$ 291.9M
PROCYSBI	\$ 189.9M
ACTIMMUNE	\$ 117.2M
UPLIZNA	\$ 60.8M

PENNSAID 2%®	\$ 191.6M
DUEXIS®	\$ 74.0M
RAYOS®	\$ 56.9M
VIMOVO®	\$ 8.4M

2021 NET SALES \$ **3,226.4M**

Science Growth

The Viela Bio acquisition brought Horizon not only a marketed medicine in UPLIZNA but dramatically expanded our pipeline with Viela's mid-stage biologics pipeline of four candidates in nine development programs. We also welcomed Viela's talented R&D team with deep early-stage research and clinical development capabilities. In September, we announced new development programs in five additional indications for two of our development-stage medicines, daxdilimab (HZN-7734) and dazodalibep (HZN-4920), further expanding our pipeline. We successfully completed two trials and initiated seven trials in 2021, followed by another in January 2022, a Phase 2b trial to evaluate the development-stage medicine HZN-825 for idiopathic pulmonary fibrosis (IPF) a rare, progressive and frequently fatal lung disease. Our pipeline, balanced across the development life cycle, now includes more than 20 programs. In all, eight data readouts from Horizon programs are expected in 2022-2023.

In addition to our expanding pipeline, we're also growing our science through internal research and outside partnerships. In June, we entered into a global collaboration and licensing agreement with Arrowhead Pharmaceuticals for the clinical development and commercialization of ARO-XDH, a potential RNA interference (RNAi)

therapeutic treatment for uncontrolled gout. In December, we entered into an agreement with Alpine Immune Sciences, a developer of immunotherapy candidates using protein engineering technologies. As part of this partnership, Horizon will have exclusive rights to develop and market up to four preclinical candidates — a lead candidate, plus others the companies may generate together through a research collaboration — for the potential treatment of autoimmune and inflammatory diseases.

Of course, scientists and researchers need space to innovate, and we're growing there, too. Just after the new year, we announced plans to lease a 192,000-square-foot facility in Rockville, Md. that's currently under construction. We expect the building to be fully operational in 2023 and will establish it as our main hub for R&D and technical operations on the East Coast, having already officially opened two other important sites in 2021: the new U.S. headquarters in Deerfield, Ill., and the new global headquarters at 70 St. Stephen's Green in Dublin, all with sustainability in mind.



Dublin



Deerfield, Ill.



Rockville, Md.

Courtesy of Alexandria Real Estate Equities, Inc.





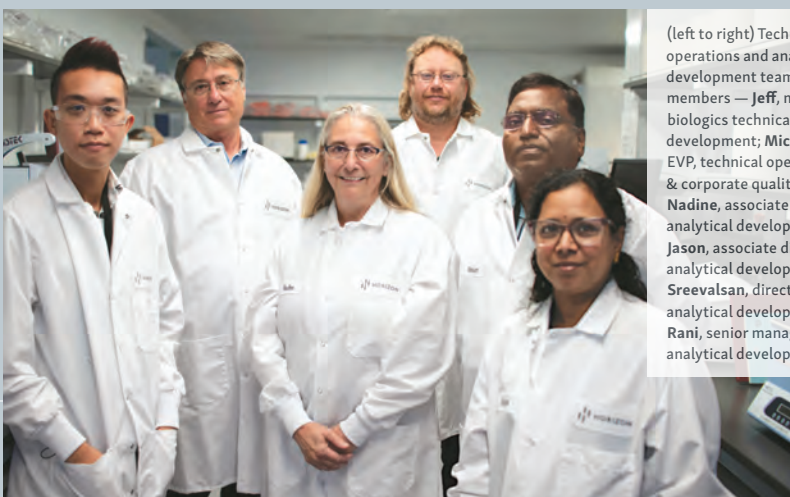
Michele, associate director, translational sciences



Sadiye, associate director, research scientist



Jodi, senior director, research

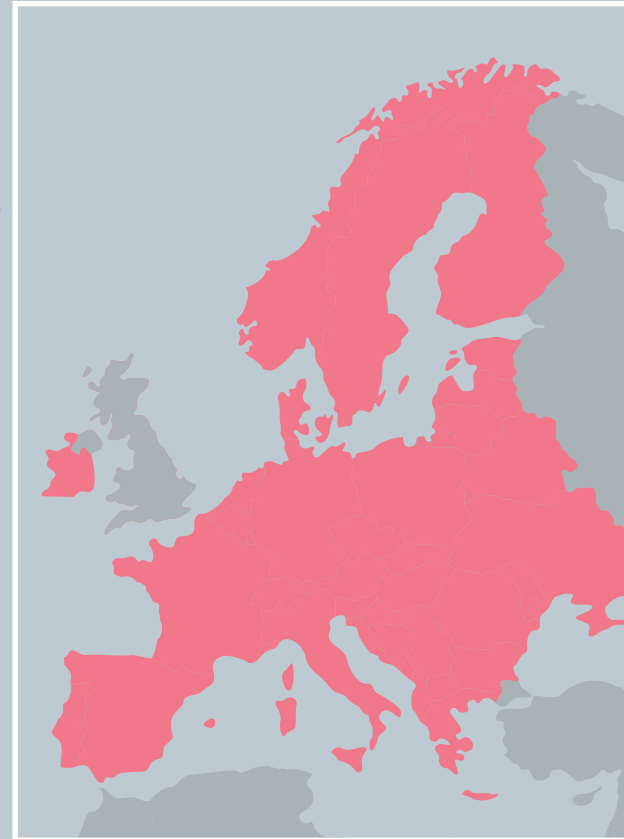


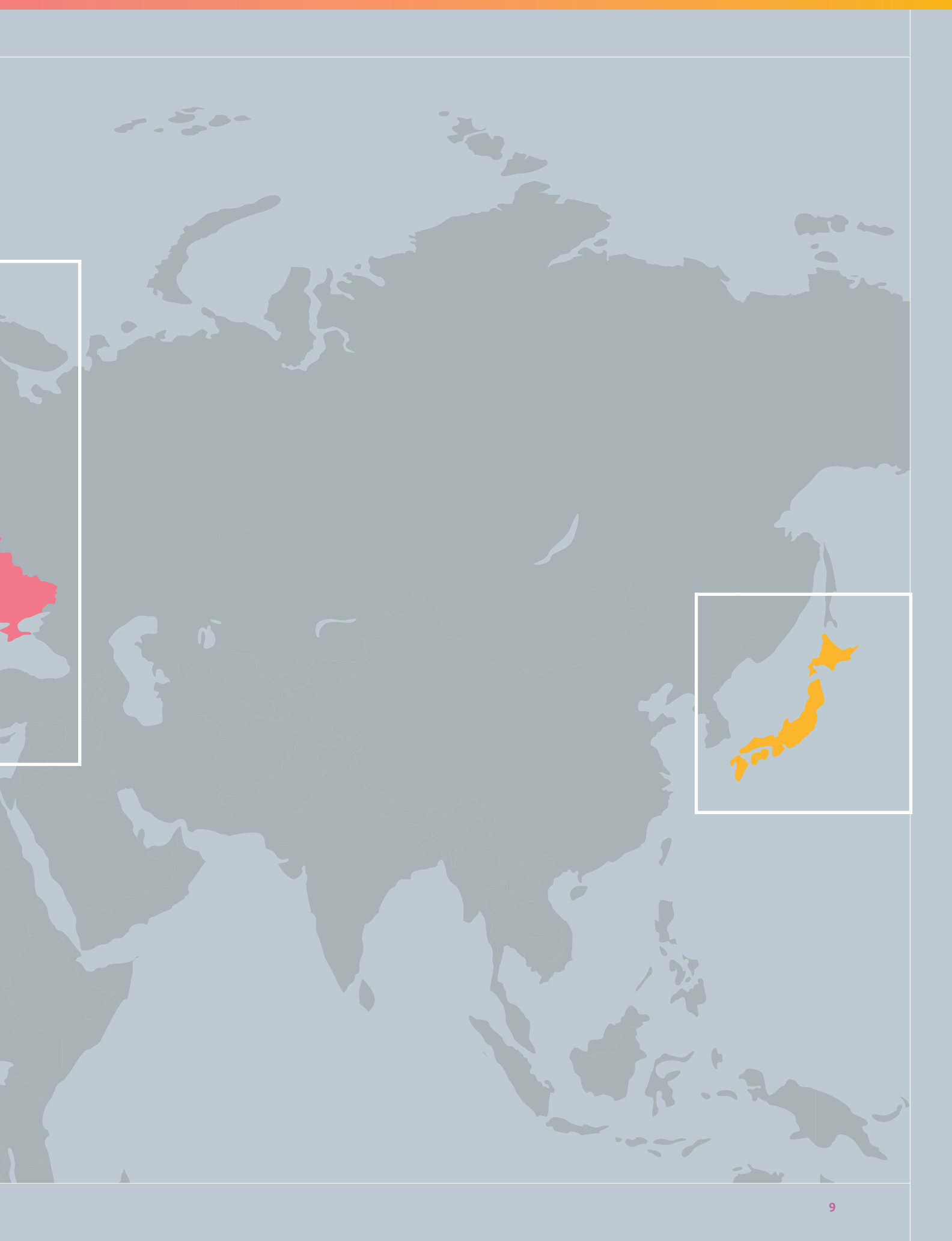
(left to right) Technical operations and analytical development team members — Jeff, manager, biologics technical development; Michael, EVP, technical operations & corporate quality; Nadine, associate director, analytical development; Jason, associate director, analytical development; Sreevalsan, director, analytical development; Rani, senior manager, analytical development

Global Growth

Last year also marked our expansion into Europe and Japan. We received a positive CHMP opinion for UPLIZNA that is considered a key step toward gaining regulatory approval to bring the medicine into Germany, France and other European markets. In Europe, we also began putting down roots by establishing infrastructure. As a result of efforts such as these, we expect 2022 to be a launch year for UPLIZNA in key international markets. Additionally, in February 2022, the first patient enrolled in a Phase 3 trial in Japan to evaluate TEPEZZA in patients with moderate-to-severe active TED. We also presented at key TED congresses in the country, reaching about 700 clinicians as we worked to improve education about the disease.

And then there's the manufacturing component of this global work: we acquired a 44,000-square-foot drug product manufacturing facility in Waterford, Ireland, about two hours from our Dublin headquarters. Following regulatory approvals, the site will give us our first in-house manufacturing capabilities for commercial supplies of TEPEZZA, KRYSTEXXA and UPLIZNA, as well as other Horizon biologic medicines for clinical trials.





Employee & Cultural Growth

Now back to where we started: the personal touch and commitment that is the lifeblood of what we do at Horizon. That starts with our employees — how we invest in them, support them and empower them to be part of our impact outside the company.

Are they satisfied and inspired? The evidence speaks for itself: 15 recognitions for Horizon in 2021 for being a top workplace, including a ranking of 36th on Fortune’s “Best Workplaces for Women” list and 16th on Fortune’s “Best Workplaces for Millennials” list, largely as a result of increased benefits and wellness offerings and enhanced opportunities for talent

development. Fortune and Great Place to Work also named Horizon No. 1 among the Best Workplaces in Biopharma for the second time since 2018.

At Horizon, we’re especially mindful of growing around the concepts of diversity, equity, inclusion and allyship (DEIA). To that end, we started 2021 by designating it our “Year of Inclusion,” with heightened focus on DEIA communication and training activities. We held 14 diverse employee community events to commemorate historical milestones, creating safe spaces for connection and enhancing employee awareness and education. We also conducted a second pay equity study, confirming what’s an enormous point of pride for us but unfortunately uncommon in the business world: Our employees are paid equitably regardless of gender or ethnicity, even as our workforce has grown significantly.

How significantly? We expanded from approximately 1,400 employees at the start of 2021 to about 1,900 by the end of the year.





Community & Reputational Growth

With a workforce that's growing rapidly, and with equity, philanthropy and personal connections guiding us, there's so much more we can do — and we did a lot of it in 2021, especially involving patient communities.

The #RAREis program, which elevates the voices, faces and experiences of people living with rare diseases, saw a nearly 70 percent increase in #RAREis Scholarship applications last year and granted nearly \$300,000 in scholarships, representing 54 different rare disease states. Students living with these diseases know they have the support of Horizon and are becoming increasingly aware of the resources and support we can potentially provide.

Besides education, Horizon and #RAREis are also opening doors for the growth of families. More than 40 children with rare diseases have been adopted to date through the #RAREis Adoption Fund, which has fast become a conduit to finding permanent homes for some of the hardest children to place.

Patients notice and appreciate our efforts to support them. **Horizon ranked No. 1 in 2021 in overall corporate reputation in a PatientView survey of U.S. patient advocacy groups who have worked with us.** These

groups cited us as the best in providing support during the COVID-19 pandemic, having a patient-centric strategy, acting with integrity and providing services beyond just our medicines.

In addition to our work with patients, our corporate social responsibility (CSR) efforts — fueled in part by employee volunteerism and contributions — have further underscored that Horizon isn't just a company with nearby offices but part of the very fabric of its surrounding communities. Consider just this short list of what we achieved in 2021 in CSR:



We donated more than \$1.1 million to eligible nonprofits through our employee donation match program and equity donation program, as well as more than 175,000 airline miles to Make-A-Wish through the Miles+ program.



In partnership with MIT Solve, we launched the Horizon Prize, a first-of-its kind global challenge focused this year on speeding diagnosis and care for people impacted by rare disease. Applicants from 22 countries, including visionaries, academics and inventors, responded to the inaugural challenge question: "How can technology help people with rare diseases get the right care faster and more accurately?" Two winners shared \$150,000 in funding to continue evolving their solutions for reducing the time it takes to be diagnosed with a rare disease.



As part of our ever-growing Horizon Scholars program, we added \$140,000 in scholarships to support 14 low-income students at Trinity College in Dublin and the Waterford (Ireland) Institute of Technology, in addition to expanding the program to include three new historically Black colleges and universities in the U.S.



We made a \$100,000 seed donation to convert Emmett Till's childhood home in Chicago into the Emmett Till Museum.



At Horizon, we'll remember 2021 as the year of transformation, with so many people benefitting, both now and in the years ahead.

Growth Reimagined? Indeed.

Is this personal? Absolutely.



Timothy P. Walbert
Chairman, President and Chief Executive Officer

Executive Management



Timothy P. Walbert
Chairman, President and
Chief Executive Officer



Aaron Cox
Executive Vice President, Finance



Geoff Curtis
Executive Vice President,
Corporate Affairs and Chief
Communications Officer



Michael DesJardin
Executive Vice President,
Technical Operations
and Corporate Quality



Jane Gonnerman
Group Vice President, Corporate
Development and Chief of Staff,
Office of the CEO



Paul W. Hoelscher
Executive Vice President,
Chief Financial Officer





Vikram Karnani
Executive Vice President
and President, International



**Jeffrey D. Kent,
M.D., FACP, FACP**
Executive Vice President, Medical
Affairs and Outcomes Research



Irina Konstantinovskiy
Executive Vice President, Chief
Human Resources and Chief
Diversity Officer



Andy Pasternak
Executive Vice President,
Chief Strategy Officer



**Jeffrey W. Sherman,
M.D., FACP**
Executive Vice President,
Chief Medical Officer



**Elizabeth H.Z.
Thompson, Ph.D.**
Executive Vice President,
Research and Development



Tina Ventura
Senior Vice President,
Chief Investor Relations Officer



Keli Walbert
Executive Vice President,
U.S. Commercial

Our Pipeline

Medicine/Candidate	Potential Indication/Program				
UPLIZNA (INEBILIZUMAB-CDON)	Myasthenia Gravis (MG)				
	IgG4-Related Disease (IgG4-RD)				
DAXDILIMAB (HZN-7734)	Systemic Lupus Erythematosus (SLE)				
	Alopecia Areata (AA) ⁽¹⁾				
	Discoid Lupus Erythematosus (DLE) ⁽¹⁾				
	Lupus Nephritis (LN) ⁽¹⁾				
	Dermatomyositis (DM) ⁽¹⁾				
DAZODALIBEP (HZN-4920)	Sjögren's Syndrome				
	Rheumatoid Arthritis				
	Kidney Transplant Rejection				
	Focal Segmental Glomerulosclerosis (FSGS) ⁽¹⁾				
HZN-825	Diffuse Cutaneous Systemic Sclerosis (dcSSc)				
	Idiopathic Pulmonary Fibrosis (IPF)				
TEPEZZA (TEPROTUMUMAB-TRBW)	Thyroid Eye Disease (TED) in Japan (OPTIC-J)				
	Subcutaneous Administration				
	Diffuse Cutaneous Systemic Sclerosis (dcSSc)				
HZN-1116	Autoimmune Diseases				
ALPINE	Autoimmune Diseases				
ARO-XDH	Next-Gen Uncontrolled Gout				
HEMOSHEAR	Novel Gout Targets				

IgG4: Immunoglobulin G4.

(1) Planned programs; not yet initiated.



>20 programs
in total



7 programs
expected to
initiate in 2022



8 data readouts
anticipated in
2022-2023⁽²⁾

(2) Because the UPLIZNA
IgG4-RD trial is an event-driven
trial, the readout timing may
extend beyond 2023.



10 potential
approvals in the
second half of
the decade



4 additional
Phase 4 programs:

- TEPEZZA chronic TED
- KRSTEXXA shorter infusion duration
- KRSTEXXA monthly dosing
- KRSTEXXA retreatment



HORIZON PHARMA PLC
FORM 10-K

**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 001-35238

HORIZON THERAPEUTICS PUBLIC LIMITED COMPANY

(Exact name of Registrant as specified in its charter)

Ireland (State or other jurisdiction of incorporation or organization) 70 St. Stephen's Green Dublin 2, D02 E2X4, Ireland (Address of principal executive offices)	Not Applicable (I.R.S. Employer Identification No.) Not Applicable (Zip Code)
011 353 1 772 2100 (Registrant's telephone number, including area code) Securities registered pursuant to Section 12(b) of the Act:	

<u>Title of Each Class</u> Ordinary shares, nominal value \$0.0001 per share	<u>Trading Symbol</u> HZNP	<u>Name of Each Exchange on Which Registered</u> The Nasdaq Global Select Market
--	--------------------------------------	--

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 an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	<input checked="" type="checkbox"/>	Accelerated filer	<input type="checkbox"/>
Non-accelerated filer	<input type="checkbox"/>	Smaller reporting company	<input type="checkbox"/>
Emerging growth company	<input type="checkbox"/>		

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 by Rule 12b-2 of the Exchange Act). Yes No

The aggregate market value of the registrant's voting ordinary shares held by non-affiliates of the registrant, based upon the \$93.64 per share closing sale price of the registrant's ordinary shares on June 30, 2021 (the last business day of the registrant's most recently completed second quarter), was approximately \$20.9 billion. Solely for purposes of this calculation, the registrant's directors and executive officers and holders of 10% or more of the registrant's outstanding ordinary shares have been assumed to be affiliates and an aggregate of 2,427,888 ordinary shares held by such persons on June 30, 2021 are not included in this calculation.

As of February 23, 2022, the registrant had outstanding 229,167,089 ordinary shares.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement for the registrant's 2022 Annual General Meeting of Shareholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

HORIZON THERAPEUTICS PLC
FORM 10-K — ANNUAL REPORT
For the Fiscal Year Ended December 31, 2021

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PART I

Special Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K contains “forward-looking statements” — that is, statements related to future, not past, events — as defined in Section 21E of the Securities Exchange Act of 1934, as amended, that reflect our current expectations regarding our future growth, results of operations, business strategy and plans, financial condition, cash flows, performance, development plans and timelines, business prospects, and opportunities, as well as assumptions made by, and information currently available to, our management. Forward-looking statements include any statement that does not directly relate to a current or historical fact. Forward-looking statements generally can be identified by words such as “believe,” “may,” “could,” “will,” “estimate,” “continue,” “anticipate,” “intend,” “seek,” “plan,” “expect,” “should,” “would”, or similar expressions. These statements are based on current expectations and assumptions that are subject to risks and uncertainties inherent in our business, which could cause our actual results to differ materially from those indicated in the forward-looking statements. Factors that could cause actual results to differ materially from those indicated in the forward-looking statements include, without limitation: our ability to successfully execute our sales and marketing strategy, including continuing to successfully recruit and retain sales and marketing personnel and to successfully build the market for our medicines; our ability to build a sustainable pipeline of new medicine candidates; whether we will be able to realize the expected benefits of strategic transactions, including whether and when such transactions will be accretive to our net income; the rate and degree of market acceptance of, and our ability and our distribution and marketing partners’ ability to obtain coverage and adequate reimbursement and pricing for, our medicines from government and third-party payers; the scope and duration of impacts of the COVID-19 pandemic on our business, our industry and the economy, including impacts to supply chains and clinical trials; our ability to maintain regulatory approvals for our medicines; our ability to conduct clinical development and obtain regulatory approvals for our medicine candidates, including potential delays in initiating and completing studies and filing for and obtaining regulatory approvals and whether data from clinical studies will support regulatory approval; our need for and ability to obtain additional financing; the accuracy of our estimates regarding future financial results; our ability to successfully execute our strategy to develop or acquire additional medicines or companies, including disruption from any future acquisition or whether any acquired development programs will be successful; our ability to manage our anticipated future growth; the ability of our medicines to compete with alternative therapies, including generic medicines and new medicines that may be developed by our competitors; our ability and our distribution and marketing partners’ ability to comply with regulatory requirements regarding the sales, marketing and manufacturing of our medicines and medicine candidates; the performance of our third-party distribution partners, licensees and manufacturers over which we have limited control; our ability to obtain and maintain intellectual property protection for our medicines; our ability to defend our intellectual property rights with respect to our medicines; our ability to operate our business without infringing the intellectual property rights of others; the loss of key commercial or management personnel; regulatory developments in the United States and other countries, including potential changes in healthcare laws and regulations; and other risks detailed below in Part I — Item 1A. “Risk Factors”. Although we believe that the expectations reflected in our forward-looking statements are reasonable, we cannot guarantee future results, events, levels of activity, performance or achievement. We undertake no obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, unless required by law.

Risk Factors Summary

Our business faces significant risks and uncertainties. If any of the following risks are realized, our business, financial condition and results of operations could be materially and adversely affected. You should carefully review and consider the full discussion of our risk factors in the section titled “Risk Factors” in Part I, Item 1A of this Annual Report on Form 10-K. Set forth below is a summary list of the principal risk factors as of the date of the filing this Annual Report on Form 10-K:

- The COVID-19 global pandemic may continue to adversely impact our business, including the commercialization of our medicines, our supply chain, our clinical trials, our liquidity and access to capital markets and our business development activities.
- Our ability to generate revenues from our medicines is subject to attaining significant market acceptance among physicians, patients and healthcare payers.
- Our future prospects are highly dependent on our ability to successfully develop and execute commercialization strategies for each of our medicines. Failure to do so would adversely impact our financial condition and prospects.
- In order to increase adoption and sales of our medicines, we will need to continue developing our commercial organization as well as recruit and retain qualified sales representatives.
- Coverage and reimbursement may not be available, or reimbursement may be available at only limited levels, for our medicines, which could make it difficult for us to sell our medicines profitably.

- Our medicines are subject to extensive regulation, and we may not obtain additional regulatory approvals for our medicines.
- We are subject to ongoing obligations and continued regulatory review by the FDA and equivalent foreign regulatory agencies, and we may be subject to penalties and litigation and large incremental expenses if we fail to comply with regulatory requirements or experience problems with our medicines.
- We rely on third parties to manufacture commercial supplies of all of our medicines, and we currently intend to rely, in whole or in part, on third parties to manufacture commercial supplies of any other approved medicines. The commercialization of any of our medicines could be stopped, delayed or made less profitable if those third parties fail to provide us with sufficient quantities of medicine or fail to do so at acceptable quality levels or prices or fail to maintain or achieve satisfactory regulatory compliance.
- We face significant competition from other biotechnology and pharmaceutical companies, including those marketing generic medicines and our operating results will suffer if we fail to compete effectively.
- Clinical development of drugs and biologics involves a lengthy and expensive process with an uncertain outcome, and results of earlier studies and trials may not be predictive of future trial results.
- If we fail to develop or acquire other medicine candidates or medicines, our business and prospects would be limited.
- We are subject to federal, state and foreign healthcare laws and regulations and implementation or changes to such healthcare laws and regulations could adversely affect our business and results of operations.
- If we are unable to obtain or protect intellectual property rights related to our medicines and medicine candidates, we may not be able to compete effectively in our markets.

Item 1. Business

Unless otherwise indicated or the context otherwise requires, references to the “Company”, “we”, “us” and “our” refer to Horizon Therapeutics plc and its consolidated subsidiaries.

Overview

We are focused on the discovery, development and commercialization of medicines that address critical needs for people impacted by rare, autoimmune and severe inflammatory diseases. Our pipeline is purposeful: we apply scientific expertise and courage to bring clinically meaningful therapies to patients. We believe science and compassion must work together to transform lives.

Our Strategy

Horizon is a leading high-growth, innovation-driven, profitable biotech company. We are focused on the discovery, development and commercialization of medicines that address critical needs for people impacted by rare, autoimmune and severe inflammatory diseases. Our three strategic goals are to: (i) maximize the benefit and value of our on-market medicines through commercial execution and clinical investment; (ii) expand our pipeline through significant investment in research and development, or R&D, and business development; and (iii) build a global presence in targeted international markets. Our vision is to build healthier communities, urgently and responsibly, supported by our philosophy to make a meaningful difference for patients and communities in need. We believe this generates value for our multiple stakeholders, including our shareholders.

We have made tremendous progress since our beginnings as a public company in 2011, when we had two on-market medicines and total net sales of \$6.9 million. With 2021 total net sales of \$3.2 billion, we now have a portfolio of 12 on-market medicines with three key growth drivers, a growing pipeline of more than 20 programs and a strong financial position that gives us the capacity to support future pipeline expansion opportunities.

We have achieved our transformation into an innovation-driven biotech company through our strong strategic execution and by leveraging the three elements we believe set Horizon apart: (i) our excellence in commercial execution; (ii) our proven and disciplined business development strategy; and (iii) our strong clinical development capability. Our excellence in commercial execution has accelerated our growth trajectory and allowed us to pursue maximizing the potential of our medicines. Through our strong in-house business development capability, we acquire and license medicines focused on opportunities for which we believe we are uniquely positioned to drive value. We leverage our deep collective drug development experience and agile approach to continually explore new ways for patients to benefit from our existing medicines and develop new medicines.

We have two reportable segments, (i) the orphan segment, our strategic growth business, and (ii) the inflammation segment, and we report net sales and segment operating income for each segment.

Our Company

We are a public limited company formed under the laws of Ireland. We operate through a number of U.S. and other international subsidiaries with principal business purposes of performing R&D or manufacturing operations, serving as distributors of our medicines, holding intellectual property assets or providing us with services and financial support.

Our principal executive offices are located at 70 St. Stephen's Green, Dublin 2, D02 E2X4, Ireland and our telephone number is 011 353 1 772 2100. Our website address is www.horizontherapeutics.com. 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.

Acquisitions and Divestitures

Since January 1, 2019, we completed the following acquisitions and divestitures:

- In July 2021, we completed the purchase of a biologic drug product manufacturing facility from EirGen Pharma Limited, or EirGen, a subsidiary of OPKO Health, Inc., in Waterford, Ireland.
- In March 2021, we completed the acquisition of Viela Bio, Inc., or Viela, in which we acquired all of the issued and outstanding shares of Viela's common stock.
- In October 2020, we sold our rights to develop and commercialize RAVICTI® and BUPHENYL® in Japan to Medical Need Europe AB, part of the Immedica Group, or Immedica. We have retained the rights to RAVICTI and BUPHENYL in North America.
- In April 2020, we acquired Curzion Pharmaceuticals, Inc., or Curzion, a privately held development-stage biopharma company, and its development-stage oral selective lysophosphatidic acid 1 receptor (LPA₁) antagonist, CZN001 (renamed HZN-825), for an upfront payment with additional payments contingent on the achievement of development and regulatory milestones.
- In June 2019, we sold our rights to MIGERGOT to Cosette Pharmaceuticals, Inc., for an upfront payment and potential additional contingent consideration payments.
- Effective January 2019, we amended our license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura Group plc, or Vectura. Under these amendments, our rights to LODOTRA® in Europe were transferred to Vectura.

The consolidated financial statements presented herein include the results of operations of the acquired businesses from the applicable dates of acquisition. Refer to Note 4, *Acquisitions, Divestitures and other Arrangements*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K, for further details of our acquisitions and divestitures.

Impact of COVID-19

Beginning in March 2020, many states and municipalities in the United States took aggressive actions to reduce the spread of the COVID-19 pandemic, including limiting non-essential gatherings of people, ceasing all non-essential travel, ordering certain businesses and government agencies to cease non-essential operations at physical locations and issuing “shelter-in-place” orders which directed individuals to shelter at their places of residence (subject to limited exceptions). Similarly, the Irish government limited gatherings of people and encouraged employees to work from their homes. Vaccines and treatments have now enabled a resumption of more normal business practices and initiatives in many countries, including the United States and Ireland. While our financial results during the year ended December 31, 2021 were strong and we continue to have a significant amount of available liquidity, the COVID-19 pandemic may continue to have a negative impact on net sales during 2022, including due to the emergence of new variants of the virus and potential actions to combat their transmission. In addition, our clinical trials have been and may in the future be affected by the COVID-19 pandemic as referred to below.

Economic and health conditions in the United States and across most of the world are continuing to change rapidly because of the COVID-19 pandemic. Although COVID-19 is a global issue that is altering business and consumer activity, the pharmaceutical industry is considered a critical and essential industry in the United States and many other countries and, therefore, we do not currently expect any government-imposed extended shut downs of suppliers or distribution channels, although our suppliers and other third parties on which we rely could be impacted by employee absences due to COVID-19 illnesses. In respect of our medicines, we believe we have sufficient inventory of raw materials and finished goods and we expect patients to be able to continue to receive their medicines at a site of care, for our infused medicines, and from their current pharmacies, alternative pharmacies or, if necessary, by direct shipment from our third-party providers that have such capability, for our other medicines.

TEPEZZA®

The launch of our infused medicine for thyroid eye disease, or TED, TEPEZZA, which was approved by the U.S. Food and Drug Administration, or FDA, on January 21, 2020, significantly exceeded our expectations. In early 2019, we initiated our pre-launch disease awareness, market development and market access efforts with multi-functional field-based teams beginning to engage with key stakeholders in July 2019. We believe these pre-launch efforts, the severity and acute nature of TED, and a highly motivated patient population have generated significant demand for the medicine. While we experienced a much higher number of new patients in 2020 than our initial estimates, the impact from COVID-19 slowed the generation of TEPEZZA patient enrollment forms, which drive new patient starts.

In December 2020, pursuant to the Defense Production Act of 1950, or DPA, Catalent Indiana, LLC, or Catalent, was ordered to prioritize certain COVID-19 vaccine manufacturing, resulting in the cancellation of previously guaranteed and contracted TEPEZZA drug product manufacturing slots, which were required to maintain TEPEZZA supply. To offset the reduced slots, we accelerated plans to increase the production scale of TEPEZZA drug product at Catalent.

In March 2021, the FDA approved a prior approval supplement to the TEPEZZA biologics license application, or BLA (which was previously approved in January 2020), giving us authorization to manufacture more TEPEZZA drug product in a batch resulting in an increased number of vials with each manufacturing slot. We commenced resupply of TEPEZZA to the market in April 2021. In addition, we received FDA approval in December 2021 for a second drug product manufacturer, Patheon Pharmaceuticals Inc., or Patheon (contract development and manufacturing organization services of Thermo Fisher Scientific). During the third quarter of 2021, we were informed that one of our contract manufacturers for TEPEZZA is manufacturing an adjuvant for a COVID-19 vaccine. The adjuvant is being manufactured on a different line to the line used to manufacture our medicine. We do not expect the manufacturing of this adjuvant to impact the supply of our medicine. Other than Catalent and the other previously mentioned contract manufacturer, we are not aware of any manufacturing facilities that are part of the supply chain for our medicines that are being utilized for the manufacture of vaccines for COVID-19. At this time, we consider our medicine inventories on hand to be sufficient to meet our commercial requirements.

As a result of the prior supply disruption, we delayed the start of an FDA-required post-marketing study to evaluate safety of TEPEZZA in a larger patient population and retreatment rates relative to how long patients receive the medicine. The FDA-required post-marketing study was initiated in the fourth quarter of 2021. We also delayed the start of our planned TEPEZZA clinical trial in chronic TED and an exploratory trial of TEPEZZA in diffuse cutaneous systemic sclerosis. The TEPEZZA clinical trial in chronic TED was initiated in the third quarter of 2021, and the exploratory trial of TEPEZZA in diffuse cutaneous systemic sclerosis was initiated in the fourth quarter of 2021.

KRYSTEXXA® and UPLIZNA®

KRYSTEXXA is an infused medicine for uncontrolled gout and was also achieving rapid growth prior to the COVID-19 pandemic. While the vast majority of patients on therapy maintained therapy, many new patients delayed infusions due to shelter-in-place guidelines and patients voluntarily delaying visits to healthcare providers and infusion centers. While there continues to be some impact on demand for KRYSTEXXA, we have seen improvements as healthcare systems have adapted to cope with the pandemic and vaccines have been widely administered in the United States.

UPLIZNA is an infused medicine for neuromyelitis optica spectrum disorder, or NMOSD, and was acquired through the Viela acquisition in March 2021. While there continues to be some impact on demand for UPLIZNA primarily due to limited patient access to healthcare providers and infusion centers, we have also seen improvements as healthcare systems have adapted to cope with the pandemic and vaccines have been widely administered in the United States.

Our other medicines

Our other orphan segment medicines, RAVICTI, PROCYSBI® and ACTIMMUNE®, treat serious, chronic diseases with serious consequences if left untreated. It is therefore critical for patients to maintain therapy. Patient motivation to continue treatment is high, and therefore net sales for these three medicines were stable during 2020 and 2021, with less impact from COVID-19 compared to our other medicines.

In regard to the inflammation segment, the impact of COVID-19 has significantly waned as healthcare systems have adapted to cope with the pandemic and vaccines have been widely administered in the United States, thereby facilitating the return to mainly in-person engagement by our sales representatives with healthcare providers. In addition, with our HorizonCares program, most patients do not need to physically visit a pharmacy to obtain a prescription because the vast majority of these medicines are delivered to a patient's home through mail or local courier, depending on the participating pharmacy.

Clinical trials

Our clinical trials have been and may in the future be affected by COVID-19 or its variants. As referred to above, certain clinical trials for TEPEZZA were delayed due to the impact of the TEPEZZA supply disruption at Catalent. In addition, clinical site initiation and patient enrollment may be delayed due to staffing shortages or prioritization of hospital and healthcare resources toward COVID-19. Current or potential patients in our ongoing or planned clinical trials may also choose to not enroll, not participate in follow-up clinical visits or drop out of the trial as a result of, or a precaution against, contracting COVID-19. Further, some patients may not be able or willing to comply with clinical trial protocols if quarantines impede patient movement or interrupt healthcare services. Some clinical sites in the United States have slowed or stopped further enrollment of new patients in clinical trials, denied access to site monitors or otherwise curtailed certain operations. Similarly, our ability to recruit and retain principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19, may be adversely impacted. These events could delay our clinical trials, increase the cost of completing our clinical trials and negatively impact the integrity, reliability or robustness of the data from our clinical trials.

We are continuing to actively monitor the possible impacts from the COVID-19 pandemic, including the emergence of new variants of the virus, and may take further actions to alter our business operations as may be required by federal, state or local authorities or that we determine are in the best interests of patients. There is significant uncertainty about the duration and potential impact of the COVID-19 pandemic. This means that our results could change at any time and the contemplated impact of the COVID-19 pandemic on our business results and outlook represents our estimate based on the information available as of the date of this Annual Report on Form 10-K.

Our Medicines

We believe our medicines address unmet therapeutic needs in orphan diseases, arthritis, pain and inflammation, and inflammatory diseases and provide significant advantages over existing therapies.

As of December 31, 2021, our commercial portfolio consisted of the following medicines:

Medicine	Indication	2021 Net Sales (in millions)	Marketing Rights
ORPHAN SEGMENT:			
TEPEZZA	Thyroid eye disease	\$ 1,661.3	Worldwide
KRYSTEXXA	Chronic refractory gout (“uncontrolled gout”)	\$ 565.5	Worldwide
RAVICTI	Urea cycle disorders	\$ 291.9	North America ⁽¹⁾
PROCYSBI	Nephropathic cystinosis	\$ 189.9	United States and certain other countries ⁽²⁾
ACTIMMUNE	Chronic granulomatous disease and severe, malignant osteopetrosis	\$ 117.2	United States, Canada and Japan ⁽³⁾
UPLIZNA	Neuromyelitis optica spectrum disorder	\$ 60.8	Worldwide, except certain countries in Asia ⁽⁴⁾
BUPHENYL	Urea cycle disorders	\$ 7.9	North America ⁽⁵⁾
QUINSAIR™	Treatment of chronic pulmonary infections due to <i>Pseudomonas aeruginosa</i> in cystic fibrosis patients	\$ 1.0	Canada and certain other countries ⁽⁶⁾
INFLAMMATION SEGMENT:			
PENNSAID 2%®	Pain of osteoarthritis of the knee(s)	\$ 191.6	United States
DUEXIS®	Signs and symptoms of osteoarthritis and rheumatoid arthritis	\$ 74.0	Worldwide
RAYOS®	Rheumatoid arthritis, polymyalgia rheumatic, systemic lupus erythematosus and multiple other indications	\$ 56.9	North America ⁽⁷⁾
VIMOVO®	Signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis	\$ 8.4	United States

- (1) In December 2018 and October 2020, we sold our rights to develop and commercialize RAVICTI outside of North America to Immedica. We have retained the rights to RAVICTI in North America.
- (2) We market PROCYSBI in the United States and Canada. We also have marketing rights to PROCYSBI in Asia. PROCYSBI is also available in Latin America through a managed assistance program through our partner Uno Healthcare Inc.
- (3) ACTIMMUNE is known as IMUKIN outside the United States, Canada and Japan. In July 2018, we sold the rights to IMUKIN in all territories outside of the United States, Canada and Japan to Clinigen Group plc.
- (4) Our strategic partner, Mitsubishi Tanabe Pharma Corporation, or MTPC, has rights to the development and commercialization of UPLIZNA for NMOSD as well as other potential future indications in Japan and certain other countries in Asia. In March 2021, MTPC received manufacturing and marketing approval for UPLIZNA in Japan. UPLIZNA was launched in Japan during the second quarter of 2021. In addition, Hansoh Pharmaceutical Group Company Limited has rights to the development and commercialization of UPLIZNA for NMOSD as well as other potential future indications in China, Hong Kong and Macau.
- (5) BUPHENYL is known as AMMONAPS outside of North America and Japan. In December 2018 and October 2020, we sold our rights to develop and commercialize BUPHENYL outside of North America to Immedica. We have retained the rights to BUPHENYL in North America.
- (6) We market QUINSAIR in Canada. We also have marketing rights for QUINSAIR in the United States, Latin America and Asia. We have not received regulatory approval to market QUINSAIR in the United States.

- (7) Outside the United States, RAYOS is sold and marketed as LODOTRA. Effective January 2019, we amended our license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura. Under these amendments, our rights to LODOTRA in Europe were transferred to Vectura.

Information on our total revenues by product in each of the years ended December 31, 2021, 2020 and 2019, is included in the section titled “Management’s Discussion and Analysis of Financial Condition and Results of Operations” in this Annual Report on Form 10-K.

ORPHAN SEGMENT

Our orphan segment consists of our medicines TEPEZZA, KRYSTEXXA, RAVICTI, PROCYSBI, ACTIMMUNE, UPLIZNA, BUPHENYL and QUINSAIR.

TEPEZZA

TEPEZZA is a fully human monoclonal antibody and a targeted inhibitor of the insulin-like growth factor-1 receptor, or IGF-1R, that is the first and only FDA-approved medicine for the treatment of TED. TED is a serious, progressive and vision-threatening rare autoimmune condition. While TED often occurs in people living with hyperthyroidism or Graves’ disease, it is a distinct disease that is caused by autoantibodies activating an IGF-1R-mediated signaling complex on cells within the retro-orbital space. This leads to a cascade of negative effects, which may cause long-term, irreversible eye damage. As TED progresses, it causes serious damage – including proptosis (eye bulging), strabismus (misalignment of the eyes) and diplopia (double vision) – and in some cases can lead to blindness. Historically, patients have had to live with TED until the inflammation subsides, after which they are often left with permanent and vision-impairing consequences and may require multiple surgeries that do not completely return the patient to their pre-disease state.

Our comprehensive post-launch commercial strategy for TEPEZZA aims to enable more TED patients to benefit from TEPEZZA. We are doing this by: (i) facilitating continued TEPEZZA uptake in the treatment of TED through continued promotion of TEPEZZA to treating physicians; (ii) continuing to develop the TED market by increasing physician awareness of the disease severity and the urgency to diagnose and treat it, as well as the benefits of treatment with TEPEZZA; (iii) driving accelerated disease identification and time to treatment through our digital and broadcast marketing campaigns; (iv) enhancing the patient journey with our high-touch, patient-centric model as well as support for the patient and site-of-care referral processes; and (v) pursuing more timely access to TEPEZZA for TED patients.

To advance the continued strong growth and adoption of TEPEZZA, we are continuing to invest in significant expansion efforts in multiple areas: our commercial and field-based organization for TEPEZZA; our marketing initiatives; our long-term supply capacity; and our efforts to expand outside the United States.

With the U.S. launch of TEPEZZA in 2020 and the demonstrated benefit to U.S. patients with TED, we are pursuing a global expansion strategy to bring TEPEZZA to patients with TED in other parts of the world. Japan is one of the countries we are pursuing and, in February 2022, we initiated a Phase 3 randomized, placebo-controlled clinical trial for the treatment of moderate-to-severe active TED patients in Japan.

As the only FDA-approved medication for the treatment of TED, TEPEZZA has no direct approved competition. We believe that the results of the TEPEZZA Phase 3 and Phase 2 clinical trials present a significantly high hurdle for potential competitors, given that potentially competitive medicines would be expected to demonstrate similar or greater efficacy and safety in the treatment of TED. In addition, we have a biologic exclusivity in the United States covering TEPEZZA that will expire in 2032. Further, the complexity of manufacturing TEPEZZA could pose a barrier to potential biosimilar competition. Although TEPEZZA does not face direct competition, other therapies, such as corticosteroids, have been used on an off-label basis to alleviate some of the symptoms of TED. While these therapies have not proved effective in treating the underlying disease, and carry with them potential significant side effects, their off-label use could reduce or delay treatment with TEPEZZA among the addressable patient population. Immunovant Inc., or Immunovant, is conducting Phase 2 clinical trials of a fully human anti-FcRn monoclonal antibody candidate for the treatment of active TED, also referred to as Graves’ ophthalmopathy. On February 2, 2021, Immunovant announced a voluntary pause in the clinical dosing of the candidate due to elevated total cholesterol and low-density lipoprotein levels in patients treated with the candidate. Immunovant has indicated it intends to continue developing the candidate but did not provide an estimate of when the dosing might resume. Viridian Therapeutics, Inc. is pursuing development of two anti-IGF-1R monoclonal antibodies for TED and initiated a Phase 1/2 trial in the fourth quarter of 2021.

KRYSTEXXA

A PEGylated uric acid specific enzyme (uricase), KRYSTEXXA is the first and only FDA approved medicine for the treatment of uncontrolled gout. Uncontrolled gout occurs in patients who have failed to normalize serum uric acid, or sUA, and whose signs and symptoms are inadequately controlled with conventional therapies, such as xanthine oxidase inhibitors, or XOIs, at the maximum medically appropriate dose, or for whom these drugs are contraindicated.

KRYSTEXXA has a unique mechanism of action that can rapidly reverse disease progression. Unlike conventional XOI therapies, which address the over-production or under-excretion of uric acid, KRYSTEXXA converts uric acid into allantoin, a water-soluble molecule, which the body can easily eliminate through the urine. Renal excretion of allantoin is ten times more efficient than uric acid excretion. Additionally, many chronic kidney disease, or CKD, patients have gout, and the disease tends to be more prevalent as CKD advances. While conventional XOI gout therapies can place additional burden on the kidneys and have dosing limitations, KRYSTEXXA has been proven effective and safe for uncontrolled gout patients with CKD without the need to adjust dosing.

Gout is one of the most common forms of inflammatory arthritis and can be assessed by a simple blood test for the amounts of uric acid in the blood (sUA levels). Typically in gout, when uric acid levels are greater than 6.8 milligrams per deciliter, urate will crystallize and deposit. These hard deposits are known as tophi and may occur anywhere in the body, including joints, as well as organs, such as the kidney and heart. When under-treated medically, tophi often lead to bone erosions and loss of functional ability. Gout flares, a common characteristic of uncontrolled gout, are intensely painful. They may or may not be accompanied by tophi. A systemic disease, uncontrolled gout frequently causes crippling disabilities and significant joint damage. Of the 9.5 million gout sufferers in the United States, we estimate that greater than 100,000 patients have uncontrolled gout.

We are focused on optimizing and maximizing the benefit the medicine offers for patients as well as driving toward its peak U.S. net sales potential. Our growth strategy for KRYSTEXXA includes: (i) supporting the continued adoption of the use of KRYSTEXXA with immunomodulators to increase the complete response rate of KRYSTEXXA; (ii) increasing uptake by rheumatologists; and (iii) accelerating uptake of the medicine by nephrologists. Following positive data from our Phase 4 randomized, placebo-controlled MIRROR clinical trial that evaluated the use of KRYSTEXXA plus methotrexate, an immunomodulator frequently used by rheumatologists, we submitted a supplemental biologics license application to the FDA in the first quarter of 2022 to expand the label for KRYSTEXXA to include co-treatment with methotrexate.

In 2019, we added a separate group of sales representatives to call exclusively on nephrologists. We believe KRYSTEXXA offers a solution to a clinical need experienced by many nephrologists in dealing with uncontrolled gout patients with CKD.

As the only FDA-approved medication for the treatment of uncontrolled gout, KRYSTEXXA faces limited direct competition. We believe that the complexity of manufacturing KRYSTEXXA provides a barrier to potential biosimilar competition. In addition, we submitted a supplemental BLA for KRYSTEXXA in the first quarter of 2022 as a result of our topline clinical results of our MIRROR randomized controlled trial evaluating KRYSTEXXA and methotrexate versus KRYSTEXXA alone. However, a number of competitors have medicines in clinical trials, including Selecta Biosciences Inc., or Selecta, which has initiated a Phase 3 clinical program of a candidate for the treatment of chronic refractory gout. In September 2020, Selecta announced topline clinical data that did not meet the primary endpoint or demonstrate statistical superiority for its Phase 2 trial that compared its candidate, which includes an immunomodulator, to KRYSTEXXA alone without an immunomodulator. In July 2020, Selecta and Swedish Orphan Biovitrum AB, or Sobi, entered into a strategic licensing agreement under which Sobi will assume responsibility for certain development, regulatory, and commercial activities for this candidate. In December 2021, Selecta and Sobi announced the completion of enrollment for DISSOLVE I, the first of two clinical studies of the Phase 3 DISSOLVE development program of SEL-212 for chronic refractory gout. SEL-212 is a combination of Selecta's ImmTOR immune tolerance platform and a therapeutic uricase enzyme (pegadricase).

RAVICTI

RAVICTI is indicated for use as a nitrogen-binding agent for chronic management of adult and pediatric patients (beginning at birth) with urea cycle disorders, or UCDs, that cannot be managed by dietary protein restriction and/or amino acid supplementation alone. UCDs are rare, life-threatening genetic disorders. RAVICTI must be used with dietary protein restriction and, in some cases, dietary supplements (for example, essential amino acids, arginine, citrulline or protein-free calorie supplements).

UCDs are inherited metabolic diseases caused by a deficiency of one of the enzymes or transporters that constitute the urea cycle. The urea cycle involves a series of biochemical steps in which ammonia, a potent neurotoxin, is converted to urea, which is excreted in the urine. UCD patients may experience episodes during which the ammonia levels in their blood become excessively high, called hyperammonemic crises, which may result in irreversible brain damage, coma or death. We estimate that there are approximately 2,600 patients with UCDs living in the United States, including approximately 1,000 diagnosed patients. RAVICTI is not indicated for treatment of acute hyperammonemia or for N-acetylglutamate synthase (NAGS) deficiency.

UCD symptoms may first occur at any age depending on the severity of the disorder, with more severe defects presenting earlier in life. However, a prompt diagnosis and careful management of the disease can lead to good clinical outcomes.

RAVICTI competes with older-generation nitrogen scavenger medicines. In the United States, RAVICTI competes with all forms of sodium phenylbutyrate, including BUPHENYL. RAVICTI has advantages over older-generation medicines leading to better patient adherence and compliance rates, such as its better tolerability for patients. It is ingested by mouth, requires little preparation and has little taste and lower sodium content than other nitrogen scavenger medications. A few competitors have alternative medicine and treatment options in development, including a gene-therapy candidate by Ultragenyx Pharmaceutical Inc., a generic taste-masked formulation option of sodium phenylbutyrate by ACER Therapeutics Inc., an enzyme replacement for a specific UCD subtype (ARG) by Aeglea Bio Therapeutics Inc., and a mRNA-based therapeutic for a specific UCD subtype (OTC) by Arcturus Therapeutics Holdings Inc. If successful, these medicine and treatment option candidates could compete with RAVICTI.

Our strategy for RAVICTI is to drive growth through increased awareness and diagnosis of UCDs; to drive conversion to RAVICTI from older-generation nitrogen scavengers, such as generic forms of sodium phenylbutyrate, based on the medicine's differentiated benefits; to position RAVICTI as the first line of therapy; and to increase compliance rates.

In December 2018 and October 2020, we sold our rights to develop and commercialize RAVICTI outside of North America to Immedica. We previously distributed RAVICTI through a commercial partner in Europe and other non-U.S. markets. We have retained rights to RAVICTI in North America.

PROCYSBI

PROCYSBI is indicated for nephropathic cystinosis, or NC, a rare lysosomal storage disorder that results in the amino acid cystine accumulating inside the lysosomes of nearly every cell. Cystine accumulation results in the formation of crystals that lead to cell damage and death in tissues and organs throughout the body. PROCYSBI (cysteamine bitartrate) delayed-release capsules and delayed-release oral granules is the first and only FDA-approved treatment for NC with 12-hour dosing. PROCYSBI uses proprietary technology that releases cysteamine gradually, providing 12-hour continuous cystine control in adults and children 1 year of age and older. PROCYSBI granules, also called "microbeads," are composed of cysteamine bitartrate surrounded by an acid-resistant enteric coating. To work properly, PROCYSBI microbeads must dissolve and release cysteamine bitartrate in the small intestine. The coating on the microbeads helps to control where and how medicine is released by allowing the cysteamine bitartrate to pass through the acidic stomach to the alkaline environment of the small intestine. Once in the small intestine, the coating begins to dissolve and the microbeads release cysteamine bitartrate gradually. This allows PROCYSBI to control cystine levels continuously over the dosing interval. Randomized controlled clinical trials and extended treatment with PROCYSBI therapy demonstrated consistent cystine depletion as monitored by levels of the biomarker (and surrogate marker), white blood cell cystine concentration.

In NC patients, elevated cystine can lead to cellular dysfunction and death; without treatment, the disease is usually fatal by the end of the first decade of life. Cystinosis is progressive, eventually causing irreversible tissue damage and multi-organ failure, including kidney failure, blindness, muscle wasting and premature death. NC is usually diagnosed in infancy after children display symptoms to physicians, including markedly increased urination, thirst, dehydration, gastrointestinal distress, failure to thrive, rickets, photophobia and kidney symptoms specific to Fanconi syndrome. Management of cystinosis requires lifelong therapy.

In February 2020, the FDA approved PROCYSBI Delayed-Release Oral Granules in Packets for adults and children one year of age and older living with nephropathic cystinosis. The PROCYSBI Delayed-Release Oral Granules in Packets product is the same as the PROCYSBI capsules product except in respect of the packaging format. This granules in packets dosage form provides another administration option for patients, in addition to the PROCYSBI capsules. PROCYSBI Delayed-Release Oral Granules in Packets were made commercially available in April 2020.

PROCYSBI is differentiated by its ability to control cystine concentration continuously over twelve hours. Older therapies require administration of medicine every six hours. By taking PROCYSBI, patients have to dose only twice a day, providing them greater control over their medication schedule and lifestyle. Additionally, because PROCYSBI can be administered through a feeding tube or mixed with approved foods and liquids, the patient can choose a more flexible dosing regimen. PROCYSBI may also have fewer known side effects, such as less severe bad breath (halitosis) and body odor, than older-generation therapies.

We estimate that there are approximately 500-550 patients diagnosed with NC living in the United States. In addition to patients who have already been identified, we believe that a number of patients with atypical phenotypic presentation and end-stage renal disease have their condition as a result of undiagnosed late-onset NC and would benefit from treatment with PROCYSBI.

Other than PROCYSBI, three pharmaceutical products are currently approved to treat cystinosis, Cystagon[®], Cystadrops[®] and Cystaran[®]. Cystagon, an immediate-release cysteamine bitartrate capsule, is an older-generation systemic cystine-depleting therapy for cystinosis in the United States marketed by Mylan N.V., and by Orphan Europe SARL in markets outside of the United States. Cystagon is PROCYSBI's primary competitor. Cystadrops is a recently approved (2020) cysteamine ophthalmic solution indicated for the treatment of corneal cystine crystal deposits and is marketed by Recordati Rare Disease Inc. Cystaran, a cysteamine ophthalmic solution, is approved in the United States for treatment of corneal crystal accumulation in patients with cystinosis and is marketed by Leadiant Biosciences, Inc. Additionally, we are aware of an early-stage gene therapy candidate in development by AVROBIO, Inc. for the treatment of cystinosis. We believe that PROCYSBI will continue to be well received in the market and continue to expect Cystagon to be the primary competitor for PROCYSBI for the foreseeable future.

Our strategy for PROCYSBI is to drive conversion of patients from older-generation immediate-release capsules of cysteamine bitartrate; to increase the uptake of the medicine by diagnosed but untreated patients; to position PROCYSBI as a first line of therapy; and to increase compliance rates.

ACTIMMUNE

ACTIMMUNE is indicated for chronic granulomatous disease, or CGD, and severe, malignant osteopetrosis, or SMO. It is a biologically manufactured protein called interferon gamma-1b that is similar to a protein the human body makes naturally. Interferon gamma helps prevent infection in CGD patients and enhances osteoclast function in SMO patients. ACTIMMUNE is the only medicine approved by the FDA to reduce the frequency and severity of serious infections associated with CGD and for delaying disease progression in patients with SMO. ACTIMMUNE is believed to work by modifying the cellular function of various cells, including those in the immune system and those that help form bones.

CGD is a genetic disorder of the immune system. It is described as a primary immunodeficiency disorder, which means it is not caused by another disease or disorder. In people who have CGD, a type of white blood cell called a phagocyte is defective. These defective phagocytes cannot generate superoxide, leading to an inability to kill harmful microorganisms such as bacteria and fungi. As a result, the immune system is weakened. People with CGD are more likely to have certain problems, such as recurrent severe and potentially life-threatening bacterial and fungal infections and chronic inflammatory conditions. These patients are prone to developing masses called granulomas, which can occur repeatedly in organs throughout the body and cause a variety of problems. We estimate that there are approximately 1,200 patients with CGD in the United States, based on an estimated incidence of 1:200,000 live births.

SMO is a form of osteopetrosis and is sometimes referred to as marble bone disease or malignant infantile osteopetrosis because it occurs in very young children. While exact numbers are not known, it has been estimated that one out of 250,000 children are born with SMO.

ACTIMMUNE currently faces limited competition. There are additional or alternative approaches used to treat patients with CGD and SMO, including the increasing trend towards the use of bone marrow transplants in patients with CGD, however, there are currently no medicines on the market that compete directly with ACTIMMUNE. Orchard Therapeutics plc has an early-stage *ex-vivo* autologous hematopoietic stem cell gene therapy candidate in development for the treatment of X-linked chronic granulomatous disease.

Our strategy for ACTIMMUNE is to increase awareness and diagnosis of CGD; to drive utilization of ACTIMMUNE prophylaxis in newly-diagnosed CGD patients as recommended in current treatment guidelines; encourage use of ACTIMMUNE in CGD patients prior to bone marrow transplant and in symptomatic carriers of x-linked CGD; and increase compliance rates overall.

UPLIZNA

UPLIZNA is a humanized monoclonal antibody that works by binding to CD19, a cell-surface molecule broadly expressed on the surface of B cells, including plasmablasts and some plasma cells. In some autoimmune diseases, autoantibodies secreted by plasmablasts and plasma cells attack native tissues as opposed to foreign pathogens. UPLIZNA depletes these plasmablasts that may produce pathogenic autoantibodies. UPLIZNA was approved for the treatment of NMOSD by the FDA in June 2020 and by the Japanese Ministry of Health, Labour and Welfare in March 2021.

NMOSD is a rare, severe autoimmune disease in which autoantibodies produced by B cells attack the optic nerve, spinal cord and brain/brainstem, often causing permanent blindness, weakness, and/or paralysis. NMOSD is characterized by unpredictable attacks and severe disability that often occurs following the first attack, accumulating with each subsequent relapse. Thus, preventing these attacks is the primary goal for disease management. NMOSD is often misdiagnosed as multiple sclerosis, or MS, which can be problematic since some MS treatments may exacerbate NMOSD. UPLIZNA is an infused medicine that works by depleting B-cells in a targeted manner and is proven to reduce NMOSD attacks.

In Japan, our strategic partner, MTPC has the rights for development and commercialization of UPLIZNA. UPLIZNA was launched in Japan during the second quarter of 2021. In November 2021, we announced that the Committee for Medicinal Products for Human Use of the European Medicines Agency, or EMA, adopted a positive opinion recommending grant of a Centralised Marketing Authorisation, or CMA, for UPLIZNA as a monotherapy for the treatment of adult patients with NMOSD who are anti-aquaporin-4 immunoglobulin G seropositive (AQP4-IgG+). While the Committee for Orphan Medicinal Products did not recommend maintenance of the orphan designation for UPLIZNA following its review, we are continuing to invest in our European infrastructure to support a potential European launch of UPLIZNA for NMOSD, which we anticipate would begin with Germany in the second quarter of 2022, assuming the grant of a CMA by the European Commission, or EC. If granted, the CMA would be valid throughout the European Economic Area (which consists of the Member States of the European Union, Iceland, Liechtenstein and Norway).

UPLIZNA is the only approved NMOSD therapy in the United States that has demonstrated a clinically relevant and durable effect on delaying worsening of disability, with a significant reduction in hospitalization. Long-term UPLIZNA treatment has been shown to be well tolerated and provide a sustained reduction in NMOSD attack risk for four or more years. UPLIZNA faces competition from eculizumab, marketed as Soliris[®] by AstraZeneca plc, and satralizumab, marketed as Enspryng[™] by Chugai Pharmaceuticals Co., Ltd., a subsidiary of F. Hoffmann-La Roche Ltd., each for the treatment of patients with NMOSD. AstraZeneca is also conducting a Phase 3 trial with Ultomiris[®] (ravulizumab) in NMOSD and, if approved for this indication, UPLIZNA could face additional competition. UPLIZNA also faces competition from rituximab, an off-label treatment that has been used for years to treat NMOSD given the lack of an approved medicine for this disease prior to 2019.

With respect to our strategy for UPLIZNA, which leverages the successful strategies we have employed with TEPEZZA and KRYSTEXXA, our aim is to (i) increase physician awareness of the benefits of UPLIZNA for the treatment of NMOSD, and what differentiates UPLIZNA from other medicines by generating additional trial data analyses and clinical evidence; (ii) drive patient initiation and adherence, and cultivate a positive patient experience; and (iii) maximize the potential of UPLIZNA through additional indications and global expansion.

BUPHENYL

BUPHENYL tablets and BUPHENYL powder are made from granules that contain sodium phenylbutyrate as the active (chemically synthesized) ingredient and microcrystalline cellulose as a diluent.

BUPHENYL tablets for oral administration and BUPHENYL powder for oral, nasogastric, or gastrostomy tube administration are indicated as adjunctive therapy in the chronic management of patients with UCDs involving deficiencies of carbamoyl phosphate synthetase, ornithine transcarbamylase or argininosuccinic acid synthetase.

BUPHENYL is indicated for treatment of all patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first twenty-eight days of life). It is also indicated for treatment of patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy. It is important that the diagnosis be made early and treatment initiated immediately to improve clinical outcomes. BUPHENYL must be combined with dietary protein restriction and, in some cases, essential amino acid supplementation. We distribute BUPHENYL in the United States.

QUINSAIR

QUINSAIR is a formulation of the antibiotic drug levofloxacin, suitable for inhalation via a nebulizer and indicated for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adult patients with cystic fibrosis, or CF. CF is a rare, life-threatening genetic disease affecting approximately 70,000 people worldwide, and results in build-up of abnormally thick secretions that can cause chronic lung infections and progressive lung damage in many patients that eventually leads to death.

INFLAMMATION SEGMENT

Our inflammation segment includes PENNSAID 2% w/w, or PENNSAID 2%, DUEXIS, RAYOS and VIMOVO.

PENNSAID 2%

PENNSAID 2% is indicated for the treatment of pain of osteoarthritis, or OA, of the knee(s). OA is a type of arthritis that is caused by the breakdown and eventual loss of the cartilage of one or more joints.

An analgesic that is easy-to-apply topically directly to the knee, PENNSAID 2% contains diclofenac sodium, a commonly prescribed nonsteroidal anti-inflammatory drug, or NSAID, to treat OA pain, and dimethyl sulfoxide, a penetrating agent that helps ensure that diclofenac sodium is absorbed through the skin to the site of inflammation and pain. Topical NSAIDs such as PENNSAID 2% are generally viewed as safer alternatives to oral NSAID treatment because they reduce systemic exposure to a fraction of that of an oral NSAID. PENNSAID 2% is the only topical NSAID offered with the convenience of a metered-dose pump, which ensures that the patient receives the correct amount of PENNSAID 2% solution with each use. PENNSAID 2% competes primarily with the generic version of Voltaren Gel 1%, a market leader in the topical NSAID category.

DUEXIS

DUEXIS is indicated for the relief of signs and symptoms of rheumatoid arthritis, or RA, and OA and to decrease the risk of developing upper-gastrointestinal, or upper-GI, ulcers in patients who are taking ibuprofen for these indications. RA is a chronic disease that causes pain, stiffness and swelling, primarily in the joints.

DUEXIS provides a fixed-dose combination in tablet form of ibuprofen, the most widely prescribed NSAID, and famotidine, a well-established upper-GI agent used to treat dyspepsia, gastroesophageal reflux disease and active ulcers.

Fixed-dose combination therapy provides significant advantages over multiple-pill regimens: fixed-dose combinations can reduce the number of pills taken; ensure that the correct dose of each component is taken at the correct time, improving compliance; and is often associated with better treatment outcomes.

In general, DUEXIS faces competition from the separate use of NSAIDs for pain relief and upper-GI medications to address the risk of NSAID-induced ulcers. However, the prescribing information for DUEXIS states that DUEXIS should not be substituted with the single-ingredient products of ibuprofen and famotidine. DUEXIS competes with other NSAIDs, including Celebrex[®], manufactured by Pfizer Inc., and celecoxib, a generic form of the medicine supplied by other pharmaceutical companies. DUEXIS also competes with TIVORBEX[™] (indomethacin) capsules, VIVLODEX[®] (meloxicam) capsules and ZORVOLEX[®] (diclofenac) capsules marketed by Iroko Pharmaceuticals, LLC.

On August 4, 2021, following a judgment in the District Court of Delaware, which was subsequently affirmed by the Federal Circuit Court of Appeals on November 16, 2021, Alkem Laboratories, Inc., or Alkem, launched a generic version of DUEXIS in the United States. As a result, we have repositioned our promotional efforts previously directed to DUEXIS to the other inflammation segment medicines and expect that our DUEXIS net sales will continue to decrease in future periods.

RAYOS

RAYOS is a corticosteroid indicated for the treatment of multiple conditions: RA; ankylosing spondylitis, or AS; polymyalgia rheumatica, or PMR; systemic lupus erythematosus, or SLE; and a number of other conditions. We focus our promotion of RAYOS on rheumatology indications, including RA and PMR.

RAYOS is composed of an active core containing prednisone that is encapsulated by an inactive porous shell, and acts as a barrier between the medicine's active core and the patient's gastrointestinal, or GI, fluids. RAYOS was developed using Vectura's proprietary GeoClock[™] and GeoMatrix[™] technologies, for which we hold an exclusive U.S. license for the delivery of glucocorticoid, a class of corticosteroid. The delivery system enables a delayed release, synchronizing the prednisone delivery time with the patient's elevated cytokine levels, thereby taking effect at a physiologically optimal point to inhibit cytokine production, and thus significantly reducing the signs and symptoms of RA and PMR.

RA is a chronic disease that causes pain, stiffness and swelling, primarily in the joints; PMR is an inflammatory disorder that causes significant muscle pain and stiffness; SLE is a chronic autoimmune disease that primarily affects women and causes inflammation and pain in the joints and muscles as well as overall fatigue.

RAYOS competes with a number of medicines in the market to treat RA, including corticosteroids, such as prednisone; traditional disease-modifying anti-rheumatic drugs, or DMARDs, such as methotrexate; and biologic agents, such as Humira and Enbrel. The majority of RA patients are treated with DMARDs, which are typically used as initial therapy in patients with RA. Biologic agents are typically added to DMARDs as combination therapy. It is common for an RA patient to take a combination of a DMARD, an oral corticosteroid, a NSAID and/or a biologic agent. We have an exclusive license to U.S. patents and patent applications from Vectura covering RAYOS. Under our settlement agreement with Teva Pharmaceuticals Industries Limited (formerly known as Actavis Laboratories FL, Inc., which itself was formerly known as Watson Laboratories, Inc. – Florida), or Teva, Teva may enter the market on December 23, 2022, or earlier under certain circumstances. As a result, we expect our net sales for RAYOS to decline in future periods.

Outside the United States, RAYOS is sold and marketed as LODOTRA. Effective January 1, 2019, we amended our license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura. Under these amendments, our rights to LODOTRA in Europe were transferred to Vectura. We ceased recording LODOTRA revenue from January 1, 2019. See "Manufacturing, Commercial, Supply and License Agreements" below for further details of the amendments.

VIMOVO

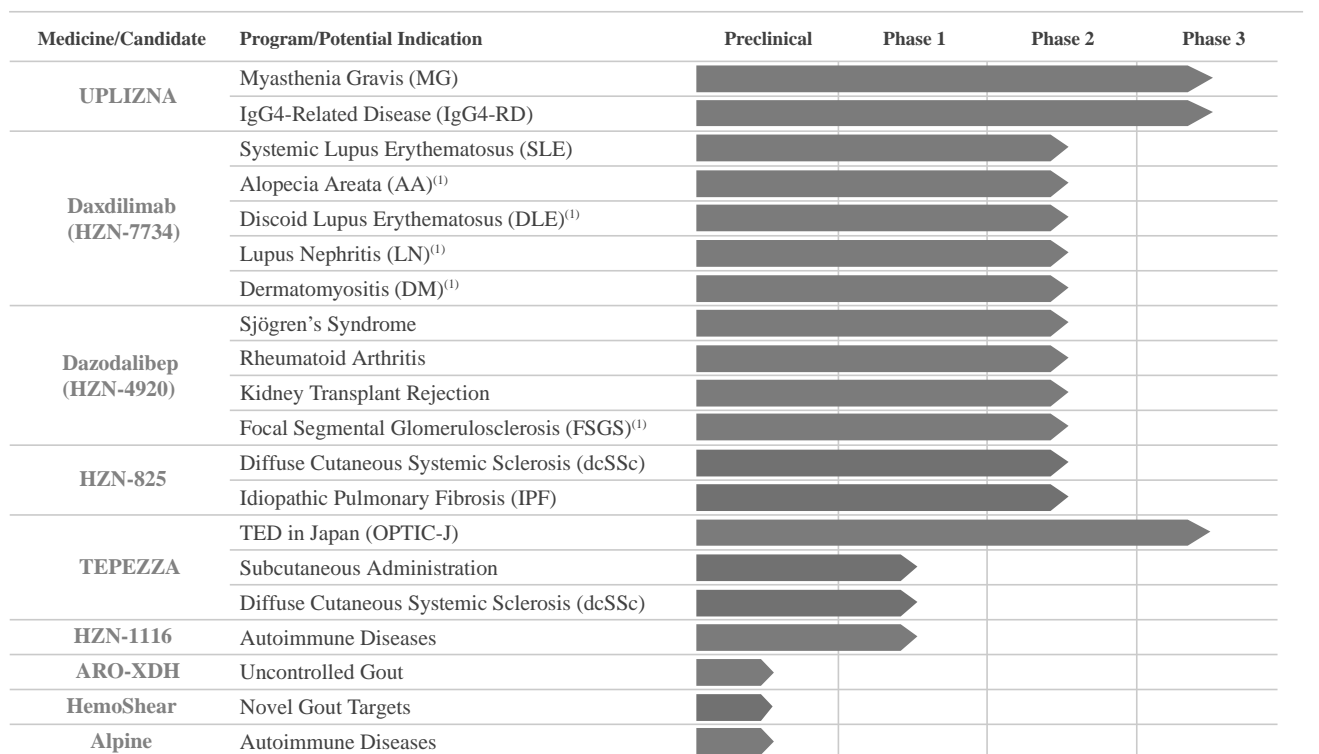
VIMOVO is indicated for the relief of signs and symptoms of OA, RA and AS and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers. It is a proprietary, fixed-dose, delayed-release tablet that combines enteric-coated naproxen, an NSAID, surrounded by a layer of immediate-release esomeprazole magnesium. Naproxen has proven anti-inflammatory and analgesic properties, and esomeprazole magnesium reduces the stomach acid secretions that can cause upper-GI ulcers. Both naproxen and esomeprazole magnesium have well-documented and excellent long-term safety profiles, and both medicines have been used by millions of patients worldwide. VIMOVO has been shown to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID associated gastric ulcers.

On February 27, 2020, following a judgment in federal court invalidating certain patents covering VIMOVO, Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratories Ltd, or collectively, Dr. Reddy's, launched a generic version of VIMOVO in the United States. While patent litigation against Dr. Reddy's for infringement continues on additional patents in the New Jersey District Court, we now face generic competition for VIMOVO, which has negatively impacted net sales of VIMOVO. As a result, we have repositioned our promotional efforts previously directed to VIMOVO to the other inflammation segment medicines and expect that our VIMOVO net sales will continue to decrease in future periods.

In addition, similar to DUEXIS, VIMOVO faces competition from the separate use of NSAIDs for pain relief and GI medications to address the risk of NSAID-induced ulcers. However, the prescribing information for VIMOVO states that VIMOVO should not be substituted with the single-ingredient products of naproxen and esomeprazole magnesium. In addition to the generic version of VIMOVO launched by Dr. Reddy's, VIMOVO also competes with other NSAIDs, including Celebrex, TIVORBEX, VIVLODEX and ZORVOLEX.

Research and Development

Our R&D programs include preclinical and clinical development of new medicine candidates, as well as development programs intended to maximize the benefit and value of our existing medicines. We devote significant resources to R&D activities that address critical unmet medical needs for people impacted by rare, autoimmune and severe inflammatory diseases. Our pipeline includes more than 20 programs, the majority of which were added in 2021. We initiated seven clinical trials in 2021 and expect to initiate seven more in 2022, including the HZN-825 IPF clinical trial initiated in January 2022 and the TEPEZZA in Japan (OPTIC-J) clinical trial initiated in February 2022. The graphic below summarizes our R&D programs ranging from preclinical to Phase 3 as of March 1, 2022.



(1) Program expected to initiate in 2022.

█ New programs added in 2021

█ Existing programs from 2020

We also have four Phase 4 programs: TEPEZZA chronic TED, KRYSTEXXA shorter infusion duration, KRYSTEXXA monthly dosing and KRYSTEXXA retreatment.

UPLIZNA Clinical Programs

UPLIZNA (inebilizumab-cdon) is an anti-CD19 humanized monoclonal antibody that depletes B cells, including the pathogenic cells that produce autoantibodies. UPLIZNA is approved by the FDA for the treatment of NMOSD. We are currently evaluating UPLIZNA in three additional indications: myasthenia gravis (a Phase 3 randomized, placebo-controlled clinical trial) and IgG4-related disease (a Phase 3 randomized, placebo-controlled clinical trial).

Daxdilimab (HZN-7734) Clinical Programs

Daxdilimab, or HZN-7734, is an anti-ILT7 human monoclonal antibody that depletes certain dendritic cells. Depleting these cells may interrupt the cycle of inflammation that causes tissue damage in diseases such as lupus, and a variety of other autoimmune conditions. We are currently evaluating daxdilimab in a Phase 2 randomized, placebo-controlled clinical trial in systemic lupus erythematosus. We expect to initiate four Phase 2 clinical trials in additional potential indications in 2022 – alopecia areata, discoid lupus erythematosus, lupus nephritis and dermatomyositis.

Dazodalibep (HZN-4920) Clinical Programs

Dazodalibep, or HZN-4920, is a CD40 ligand antagonist that blocks T cell interaction with the CD40-expressing B cells, disrupting the overactivation of the CD40 ligand co-stimulatory pathway. Several autoimmune diseases are associated with the overactivation of this pathway. Clinical trials in three indications are currently underway: a Phase 2b randomized, placebo-controlled clinical trial in Sjögren's syndrome, a Phase 2 randomized, placebo-controlled clinical trial in rheumatoid arthritis and a Phase 2 open-label clinical trial in kidney transplant rejection. We expect to initiate a Phase 2 clinical trial in focal segmental glomerulosclerosis in 2022.

HZN-825 Clinical Programs

HZN-825 is an oral selective LPAR₁ antagonist that prevents gene activation and has demonstrated antifibrotic activity. We are pursuing Phase 2b pivotal trials of HZN-825 in two potential indications – diffuse cutaneous systemic sclerosis and idiopathic pulmonary fibrosis.

TEPEZZA Clinical Programs

TEPEZZA (teprotumumab-trbw) is an IGF-1R antagonist monoclonal antibody. It is the first and only medicine approved by the FDA for the treatment of TED. Two of our three TEPEZZA clinical programs are underway: a Phase 1 pharmacokinetic clinical trial for subcutaneous administration of TED and a Phase 1 exploratory clinical trial in diffuse cutaneous systemic sclerosis. OPTIC-J, a Phase 3 randomized, placebo-controlled clinical trial for the treatment of moderate-to-severe active TED patients in Japan, was initiated in February 2022.

HZN-1116 Autoimmune Disease Program

HZN-1116 is a human monoclonal antibody designed to neutralize the FLT3-ligand, thereby reducing both conventional and plasmacytoid dendritic cells that play a key role in driving inflammatory processes. We are currently evaluating HZN-1116 in a Phase 1 clinical trial for autoimmune diseases.

Preclinical Programs

Our agreements with Arrowhead Pharmaceuticals, Inc., or Arrowhead, and HemoShear Therapeutics, LLC are both exploring the potential for novel therapeutics to address the unmet need for the more than 500,000 gout patients who do not respond to the current standard of conventional care and are not good candidates for KRYSTEXXA. Our preclinical program with Alpine Immune Sciences, Inc., or Alpine, is focused on developing novel protein-based therapies for autoimmune and inflammatory diseases. We are leveraging external collaborations for our three programs, using their specialized technologies in combination with our internal expertise.

Phase 4 TEPEZZA and KRYSTEXXA Programs

Additional programs not shown on the pipeline above include our Phase 4 TEPEZZA and KRYSTEXXA programs. Our ongoing TEPEZZA Phase 4 randomized, placebo-controlled clinical trial in chronic TED is designed to better inform physicians and payers on the safety and efficacy of TEPEZZA in patients with chronic TED. Our three Phase 4 KRYSTEXXA open-label clinical trials underway are evaluating KRYSTEXXA plus the immunomodulator methotrexate in a shorter-infusion duration trial; a monthly dosing trial; and a retreatment trial for patients who were not complete responders to KRYSTEXXA monotherapy.

Clinical Programs Completed in 2021

In 2021, we successfully completed two KRYSTEXXA clinical trials, MIRROR and PROTECT:

KRYSTEXXA MIRROR: Our Phase 4 randomized, placebo-controlled MIRROR clinical trial evaluated the use of KRYSTEXXA plus methotrexate, an immunomodulator frequently used by rheumatologists. The trial results demonstrated that 71.0 percent (71 of 100) patients randomized to receive KRYSTEXXA plus methotrexate achieved a complete response rate, defined as serum uric acid <6 mg/dL at least 80% of the time during Month 6 (p<0.0001), a significant improvement from the 38.5 percent response rate in patients (20 of 52) who were randomized to receive KRYSTEXXA plus placebo. KRYSTEXXA plus immunomodulation is a core element of our strategy to maximize the value of KRYSTEXXA and enable more patients with uncontrolled gout to benefit from the medicine. We submitted a supplemental biologics license application to the FDA in the first quarter of 2022 to expand the label for KRYSTEXXA to include co-treatment with methotrexate.

KRYSTEXXA PROTECT: Our Phase 4 open-label PROTECT clinical trial evaluated the use of KRYSTEXXA in patients with uncontrolled gout who had received a kidney transplant and were treated with two to three immunosuppressive agents to prevent organ rejection. Gout is more common and often more severe among patients who have undergone kidney transplantation. 88.9 percent (16 of 18) of the patients achieved the primary endpoint, defined as sUA <6 mg/dL for at least 80 percent of time during Month 6, demonstrating that KRYSTEXXA provided a substantial and sustained decrease in sUA for these patients.

Distribution

We use central third-party logistics and FDA-compliant warehouses for storage and distribution of our medicines into the supply chain. Our third-party logistics provider specializes in integrated operations that include warehousing and transportation services that can be scaled and customized to our needs based on market conditions and the demands and delivery service requirements for our medicines and materials. Their services eliminate the need to build dedicated internal infrastructures that would be difficult to scale without significant capital investment. Our third-party logistics provider warehouses all medicines in controlled FDA-registered facilities. Incoming orders are prepared and shipped through an order entry system to ensure adequate supply and delivery of our medicines.

Sales and Marketing

As of December 31, 2021, our sales force was composed of approximately 480 sales representatives consisting of approximately 280 orphan sales representatives and 200 inflammation sales representatives.

Our orphan sales representatives focus on marketing our rare disease medicines to a limited number of healthcare practitioners who specialize in fields such as pediatric immunology, allergy, infectious diseases, metabolic disorders, rheumatology, nephrology, ophthalmology and endocrinology, to help them understand the potential benefits of our medicines. We have entered into, and may continue to enter into, agreements with third parties to commercialize our medicines outside the United States.

We offer discount card and other programs such as our HorizonCares program to patients under which the patient receives a discount on his or her prescription. In certain circumstances when a patient's prescription is rejected by a managed care vendor, we will pay for the full cost of the prescription. Patients are able to fill prescriptions for our inflammation medicines through pharmacies participating in our HorizonCares patient assistance program, as well as other pharmacies. In addition, we have business arrangements with pharmacy benefit managers, or PBMs, and other payers to secure formulary status and reimbursement of our inflammation medicines. The business arrangements with the PBMs generally require us to pay administrative fees and rebates to the PBMs and other payers for qualifying prescriptions.

We have a comprehensive compliance program in place to address adherence with various laws and regulations relating to our sales, marketing, and manufacturing of our medicines, as well as certain third-party relationships, including pharmacies. Specifically with respect to pharmacies, the compliance program utilizes a variety of methods and tools to monitor and audit pharmacies, including those that participate in our patient assistance programs, to confirm their activities, adjudication and practices are consistent with our compliance policies and guidance.

Manufacturing, Commercial, Supply and License Agreements

We have agreements with third parties for active pharmaceutical ingredients, or APIs, biological drug substance, manufacture of our medicines, formulation and development services. We also have agreements for fill, finish and packaging services, transportation, and distribution and logistics services for certain medicines. In all cases, we retain certain levels of safety stock or maintain alternate supply relationships that we can utilize without undue disruption of our manufacturing processes if a third party fails to perform its contractual obligations.

In July 2021, we purchased a biologic drug product manufacturing facility in Waterford, Ireland, which is intended to be an additional source of manufacturing to supplement the capabilities of our third-party drug product manufacturers. We are in the process of completing the build-out and validation of this facility and assuming timely receipt of regulatory approvals, we expect that the first medicine manufactured at the facility to be approved for release in 2023.

TEPEZZA

TEPEZZA is produced by culture of a genetically engineered mammalian cell line containing the DNA which encodes for teprotumumab-trbw, a fully human IgG1 monoclonal antibody. Cell culture broth is harvested and purified through filtration processes and chromatography processes prior to being formulated, frozen and shipped to the site of drug product manufacture. In support of its manufacturing process, we store multiple vials of teprotumumab-trbw master cell bank and working cell bank at multiple locations in order to ensure adequate backup should any cell bank be lost in a catastrophic event.

AGC Biologics Supply Agreement

In February 2018, we entered into a commercial supply agreement with AGC Biologics A/S (formerly known as CMC Biologics A/S), or AGC, which was amended in May 2019, December 2019 and July 2020, for the supply of TEPEZZA drug substance from AGC's facilities in Copenhagen, Denmark and Boulder, Colorado. Pursuant to the agreement, we have agreed to purchase certain minimum annual order quantities of TEPEZZA drug substance. In addition, we must provide AGC with rolling forecasts of TEPEZZA drug substance requirements, with a portion of the forecast being a firm and binding order. The agreement has a term that runs indefinitely. Either party may terminate the agreement by giving notice at least three years in advance. Either party may also terminate the agreement for the other party's failure to pay any undisputed sum payable under the agreement within a specified period of time, for a material breach by the other party if not cured within a specified period of time, upon the other party's insolvency, or in the event that any material permit or regulatory license is permanently revoked preventing the performance of specified services by the other party.

AGC Development and Manufacturing Services Agreement

We have a development and manufacturing services agreement with AGC, dated June 10, 2015, which was amended in February 2018, for development and manufacturing services relating to TEPEZZA drug substance. The agreement has a term that runs until the later of the date that all work under the agreement is completed and June 2025, unless earlier terminated by us upon 30 days' written notice. AGC can terminate the agreement after AGC has completed its services by giving 180 days' written notice, or sooner if certain conditions are met, or upon 60 business days' notice if AGC reasonably concludes it cannot deliver the services under the agreement despite applying commercially reasonable efforts. Either party may also terminate the agreement for the other party's failure to pay any undisputed sum payable under the agreement within a specified period of time, for a material breach by the other party if not cured within a specified period of time, or upon the other party's insolvency.

Catalent Indiana Supply Agreement

In December 2018, we entered into a commercial supply agreement with Catalent, for the supply of TEPEZZA drug product. Pursuant to the agreement, we must provide Catalent with rolling forecasts of TEPEZZA drug product requirements, with a portion of the forecast being a firm and binding order. The agreement has a term that runs until December 18, 2025, and automatically renews for two successive two-year terms unless terminated by either party at least two years in advance. The agreement may be terminated earlier by either party for a material breach by the other party, if not cured within a specified period of time, or upon the other party's insolvency.

Patheon Italy Agreement

In October 2018, we entered into a master manufacturing services agreement with Patheon. Pursuant to the agreement, in June 2020, we entered into a product agreement, which was amended in October 2021, for the manufacture and supply of TEPEZZA drug product in Italy. Pursuant to the master manufacturing services agreement and the amended product agreement, or, collectively, the Patheon manufacturing agreement, we must provide Patheon a monthly rolling forecast of TEPEZZA drug product requirements, with a portion of the forecast being a firm and binding order. The Patheon manufacturing agreement has a term that runs until October 2026, and automatically renews for successive three-year terms unless terminated by either party at least two years in advance. The agreement may be terminated earlier by either party for a material breach by the other party, if not cured within a specified period of time, or upon the other party's insolvency.

Roche License Agreement

We have a license of intellectual property rights to TEPEZZA under a license agreement with Roche, effective as of June 15, 2011, as amended. Pursuant to the agreement, we have paid development and regulatory milestones totaling CHF60.0 million relating to the United States. We may be obligated to pay Roche additional development and regulatory milestones for activities outside the United States or for additional indications. We are also obligated to pay tiered royalties between 9 and 12 percent on annual worldwide net sales. The royalty terminates upon the later of (a) the expiration date of the longest-lived patent rights on a country-by-country basis; and (b) ten years after first commercial sale of TEPEZZA. Either party may terminate the agreement upon the other party's breach of the agreement, if not cured within a specified period of time, or in the event of the other party's bankruptcy or insolvency. Roche may also terminate the agreement if we challenge the validity of Roche's patents. We may also terminate the agreement with nine months written notice to Roche.

Boehringer Ingelheim Biopharmaceuticals License Agreement

We have a license of certain manufacturing technology for TEPEZZA under a license agreement with Boehringer Ingelheim Biopharmaceuticals, effective as of December 21, 2016. Either party may terminate the agreement upon the other party's material breach of the agreement if not cured within a specified period of time. Boehringer Ingelheim Biopharmaceuticals may also terminate the agreement if we challenge the validity of certain of its patent rights.

Other Agreements

In addition to the above supply and license agreements, under the agreement for the acquisition of River Vision in May 2017, we were required to pay up to \$325.0 million upon the attainment of various milestones, composed of \$100.0 million related to FDA approval and \$225.0 million related to net sales thresholds for TEPEZZA. We made a \$100.0 million milestone payment related to FDA approval during the first quarter of 2020. The agreement also included a royalty payment of 3 percent of the portion of annual worldwide net sales exceeding \$300.0 million.

In April 2020, we entered into an agreement with S.R. One, Limited, or S.R. One, and an agreement with Lundbeckfond Invest A/S, or Lundbeckfond, pursuant to which we acquired all of S.R. One's and Lundbeckfond's beneficial rights to proceeds from certain contingent future TEPEZZA milestone and royalty payments in exchange for a one-time payment of \$55.0 million to each of the respective parties. As a result of our agreements with S.R. One and Lundbeckfond in April 2020, our remaining net obligations to make TEPEZZA payments to the former stockholders of River Vision was reduced by approximately 70.25%, after including payments to a third party.

This resulted in milestone payments of \$67.0 million to the other former River Vision stockholders during the year ended December 31, 2021. There are no further TEPEZZA net sales milestone obligations remaining to the former River Vision stockholders. In addition, as a result of the S.R. One and Lundbeckfond agreements, annual earnout payments of 0.893 percent are due on the portion of annual worldwide net sales exceeding \$300.0 million.

KRYSTEXXA

KRYSTEXXA is produced by fermentation of a genetically engineered *Escherichia coli* bacterium containing the DNA which encodes for uricase. The complementary DNA coding for the uricase is based on mammalian sequences. Uricase is purified and is then PEGylated with a PEGylation agent to produce the bulk medicine, pegloticase. PEGylation and purification of the active drug substance is achieved by conventional column chromatography. The resulting highly purified sterile solution is filled in a single-use vial for intravenous infusion following dilution. In support of its manufacturing process, we store multiple vials of the *Escherichia coli* bacterium master cell bank and working cell bank at multiple locations in order to ensure adequate backup should any cell bank be lost in a catastrophic event.

NOF Supply Agreement

Under the terms of our exclusive supply agreement with NOF Corporation, or NOF, as amended, for the PEGylation agent used in the manufacture of KRYSTEXXA, we are required to issue NOF forecasts of our requirements for the PEGylation agent, a portion of which are binding. Under the agreement, we are obligated to purchase a certain minimum quantity of the PEGylation agent over specified periods of time and we are required to use NOF as our exclusive supplier for the PEGylation agent, subject to certain exceptions if NOF is unable to supply the PEGylation agent. The agreement expires in October 2024. Either we or NOF may also terminate the agreement upon a material breach, if not cured within a specified period of time, or in the event of the other party's insolvency.

Bio-Technology General (Israel) Supply Agreement

We have a commercial supply agreement, as amended, with Bio-Technology General (Israel) Ltd, or BTG Israel, for the production of the bulk KRYSTEXXA medicine, or bulk product. Under this agreement, we have agreed to purchase certain minimum annual order quantities and are obligated to purchase at least 80 percent of our annual world-wide bulk product requirements from BTG Israel. The term of the agreement runs until December 31, 2030, and will automatically renew for successive three-year periods unless earlier terminated by either party upon three years' prior written notice. The agreement may be terminated earlier by either party in the event of a force majeure, liquidation, dissolution, bankruptcy or insolvency of the other party, uncured material breach by the other party or after January 1, 2024, upon three years' prior written notice. Under the agreement, if the manufacture of the bulk product is moved out of Israel, we may be required to obtain the approval of the Israel Innovation Authority (formerly known as Israeli Office of the Chief Scientist), or IIA, because certain KRYSTEXXA intellectual property was initially developed with a grant funded by the IIA. We must provide BTG with rolling forecasts of the volume of KRYSTEXXA that we expect to order, with a portion of the forecast being a firm and binding order.

Exelead PharmaSource Supply Agreement

In October 2008, Savient Pharmaceuticals, Inc. (as predecessor in interest to Crelta Pharmaceuticals LLC) and Exelead, Inc. (formerly known as Sigma Tau PharmaSource, Inc. (as successor in interest to Enzon Pharmaceuticals, Inc.)), or Exelead, entered into a commercial supply agreement, which was subsequently amended, for the packaging and supply of the final KRYSTEXXA drug product. This agreement remains in effect until terminated, and either we or Exelead may terminate the agreement with three years notice, given thirty days prior to the agreement anniversary date. Either we or Exelead may also terminate the agreement upon a material default, if not cured within a specified period of time, or in the event of the other party's insolvency or bankruptcy.

Duke University and Mountain View Pharmaceutical License Agreement

We have a worldwide license agreement with Duke University, or Duke, and Mountain View Pharmaceuticals Inc., or MVP, which was subsequently amended. Duke developed the recombinant uricase enzyme used in KRYSTEXXA and MVP developed the PEGylation technology used in the manufacture of KRYSTEXXA. Duke and MVP may terminate the agreement if we commit fraud or for our willful misconduct or illegal conduct; upon our material breach of the agreement, if not cured within a specified period of time; upon written notice if we have committed two or more material breaches under the agreement; or in the event of our bankruptcy or insolvency. Under the terms of the agreement, we are obligated to pay Duke a mid-single digit percentage royalty on our global net sales of KRYSTEXXA and a royalty of between 5 percent and 15 percent on any global sublicense revenue. We are also obligated to pay MVP a mid-single digit percentage royalty on our net sales of KRYSTEXXA outside of the United States and royalty of between 5 percent and 15 percent on any sublicense revenue outside of the United States.

RAVICTI

RAVICTI is formed by the catalyzed esterification of glycerol with 4-phenylbutyric acid and the subsequent purification of the glycerol phenylbutyrate formed. The purified glycerol phenylbutyrate drug substance is filled into glass bottles for use as an oral dosage liquid.

We have a supply agreement with Seqens (Germany) for supply of 4-Phenylbutyric acid (4-PBA) needed to produce glycerol phenylbutyrate API. We have supplies of glycerol phenylbutyrate API manufactured for us by two alternate suppliers, Helsinn Advanced Synthesis SA (Switzerland) and Patheon Austria GmbH & Co KG (formerly DSM Fine Chemicals Austria) on a purchase-order basis until 2025. We have manufacturing agreements for finished RAVICTI drug product with Lyne Laboratories, Inc. and PCI Pharma Services.

Bausch Health Asset Purchase Agreement

We have an asset purchase agreement with Bausch Health Companies, Inc. (formerly Ucyclyd Pharma, Inc.), or Bausch, pursuant to which we are obligated to pay to Bausch mid-single-digit royalties on our global net sales of RAVICTI. The asset purchase agreement cannot be terminated for convenience by either party. We have a license to certain Bausch manufacturing technology related to RAVICTI; however Bausch is permitted to terminate the license if we fail to comply with any payment obligations relating to the license and do not cure such failure within a defined time period.

Brusilow License Agreement

We have a license agreement, as amended, with Saul W. Brusilow, M.D. and Brusilow Enterprises, Inc., or Brusilow, pursuant to which we license patented technology related to RAVICTI from Brusilow. Under such agreement, we are obligated to pay low-single digit royalties to Brusilow on net sales of RAVICTI that are, or were, covered by a valid claim of a licensed patent. The license agreement may be terminated for any uncured breach as well as bankruptcy. We may also terminate the agreement at any time by giving Brusilow prior written notice, in which case all rights granted to us would revert to Brusilow.

PROCYSBI

PROCYSBI drug product is composed of enteric-coated beads of cysteamine bitartrate encapsulated in gelatin capsules or packaged directly into packets. PROCYSBI drug product and API, cysteamine bitartrate, are manufactured and packaged on a contract basis by third parties.

Cambrex Profarmaco Milano Supply Agreement

We have an API supply agreement, as amended, with Cambrex Profarmaco Milano, or Cambrex, related to PROCYSBI API. Pursuant to the agreement, we must provide rolling, non-binding forecasts, with a portion of the forecast being the minimum floor of the firm order that must be placed. The Cambrex supply agreement has a term that runs until November 30, 2024, and which renews for successive two-year terms if not terminated at least one year in advance.

Patheon Manufacturing Services Agreement

We have a manufacturing services agreement with Patheon for the manufacture and supply of PROCYSBI capsules and granules. Pursuant to the agreement, we must provide a rolling, non-binding forecast of PROCYSBI, with a portion of the forecast being a firm written order. The agreement has a term that runs until December 31, 2023 and which automatically renews for successive two-year terms if not terminated at least eighteen months in advance. In addition, we have separate agreement with another third-party contract manufacturer for the packaging of PROCYSBI granules.

UCSD License Agreement

In May 2017, we entered into an amended and restated license agreement with The Regents of the University of California, San Diego, or UCSD, which was amended in September 2018. We must pay UCSD a royalty in the mid-single digits on net sales of PROCYSBI in countries where PROCYSBI is covered by a patent right, and a royalty in the low-single digits on net sales of PROCYSBI in countries where PROCYSBI is not covered by a patent right.

ACTIMMUNE

ACTIMMUNE is a recombinant protein that is produced by fermentation of a genetically engineered *Escherichia coli* bacterium containing the DNA which encodes for the human protein. Purification of the active drug substance is achieved by conventional column chromatography. The resulting active drug substance is then formulated as a highly purified sterile solution and filled in a single-use vial for subcutaneous injection, which is the ACTIMMUNE finished drug product. In support of its manufacturing process, we and Boehringer Ingelheim RCV GmbH & Co KG, or Boehringer Ingelheim, store multiple vials of the *Escherichia coli* bacterium master cell bank and working cell bank in order to ensure adequate backup should any cell bank be lost in a catastrophic event.

UPLIZNA

UPLIZNA is produced by culture of a genetically engineered mammalian cell line containing the DNA which encodes for inebilizumab-*cdon*, a humanized IgG1 monoclonal antibody. Cell culture broth is harvested and purified through filtration processes and chromatography processes prior to being formulated, frozen, thawed, and shipped to the site of drug product manufacture. In support of its manufacturing process, we store multiple vials of inebilizumab-*cdon* master cell bank and working cell bank at multiple locations in order to ensure adequate backup should any cell bank be lost in a catastrophic event.

We have a commercial supply agreement with AstraZeneca Pharmaceuticals LP for the manufacture and supply of UPLIZNA drug substance and drug product. The initial period of this agreement is 10 years from April 2019 and will automatically renew for separate but successive three-year terms unless 24 months advance written notice is given by either party that it does not intend to renew. We must provide AstraZeneca Pharmaceuticals LP with rolling forecasts for drug substance and drug product, with a portion of the forecasts being a firm and binding order.

OTHER MEDICINES

ORPHAN SEGMENT

BUPHENYL API is manufactured on a contract basis by a third party and final manufacturing, testing and packaging of the medicine is provided by another third party. QUINSAIR drug product, its API, levofloxacin hemihydrate, and the Zirela nebulizer device are all manufactured on a contract basis by three separate third parties.

INFLAMMATION SEGMENT

PENNSAID 2% is manufactured on a contract basis by a third party. The two APIs for DUEXIS are manufactured on a contract basis by two separate third parties. The final packaged form of DUEXIS is provided on a contract basis from an additional third party. We purchase API for RAYOS from a contract manufacturer. In addition, we have contracted with two separate third-party manufacturers for the production of RAYOS tablets and for the packaging and assembling of RAYOS. The two APIs for VIMOVO are manufactured on a contract basis by two separate third parties. The final packaged form of VIMOVO is provided on a contract basis from an additional third party.

Intellectual Property

Our objective is to aggressively patent the technology, inventions and improvements that we consider important to the development of our business. We have a portfolio of patents and applications based on our R&D, clinical and pharmacokinetic/pharmacodynamic modeling discoveries, and our novel formulations. We intend to continue filing patent applications seeking intellectual property protection as we generate discoveries from R&D, anticipated formulation refinements, new methods of manufacturing and clinical trial results.

We will only be able to protect our technologies and medicines from unauthorized use by third parties to the extent that valid and enforceable patents or trade secrets cover them. As such, our commercial success will depend in part on receiving and maintaining patent protection and trade secret protection of our technologies and medicines as well as successfully defending these patents against third-party challenges.

The patent positions of life sciences companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in such companies' patents has emerged to date in the United States. The patent situation outside the United States is even more uncertain. Changes in either the patent laws or in interpretations of patent laws in the United States or other countries may diminish the value of our intellectual property. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in our patents or in third-party patents. For example:

- we or our licensors might not have been the first to make the inventions covered by each of our pending patent applications and issued patents;
- we or our licensors might not have been the first to file patent applications for these inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies;
- it is possible that none of our pending patent applications or the pending patent applications of our licensors will result in issued patents;
- our issued patents and the issued patents of our licensors may not provide a basis for commercially viable drugs, or may not provide us with any competitive advantages, or may be challenged and invalidated by third parties;
- we may not be successful in any patent litigation to enforce our patent rights;
- we may not develop additional proprietary technologies or medicine candidates that are patentable; or
- the patents of others may have an adverse effect on our business.

TEPEZZA

We are either a licensee or owner of U.S. and foreign patents and applications covering TEPEZZA. If not otherwise invalidated, those patents expire between February 2023 and April 2039. We continue to prosecute and pursue patent protection to obtain additional patent coverage on TEPEZZA and its uses. Additionally, we have a biologic exclusivity in the United States covering TEPEZZA that will expire in 2032.

KRYSTEXXA

We have licenses to U.S. and foreign patents and applications covering KRYSTEXXA. If not otherwise invalidated, those patents expire between 2023 and 2030. We continue to prosecute and pursue patent protection to obtain additional patent coverage on KRYSTEXXA and its uses.

In the United States, KRYSTEXXA has received twelve years of biologic exclusivity, expiring on September 14, 2022.

RAVICTI

We have ownership of or licenses to U.S. and foreign patents and patent applications covering RAVICTI. If not otherwise invalidated, those patents expire between 2030 and 2036. We license our rights to patents and patent applications outside of North America to Immedica.

In the United States, RAVICTI received two separate orphan drug exclusivities for two patient populations. The first of those orphan drug exclusivities expired on February 1, 2020, and the second will expire on April 28, 2024. Under our settlement and license agreement with Par Pharmaceutical, Inc., Par Pharmaceutical, Inc. may enter the market on July 1, 2025, or earlier in certain circumstances. We also have settlement and license agreements with Lupin Limited and Lupin Pharmaceuticals, Inc., or collectively Lupin; and Annora Pharma Private Limited and Hetero USA, Inc., or collectively Annora, pursuant to which Lupin and Annora may enter the market on July 1, 2026, or earlier under certain circumstances.

PROCYSBI

We have U.S. and foreign patents and patent applications covering PROCYSBI, as well as licenses from the University of California, San Diego to U.S. and foreign patents and patent applications covering PROCYSBI. If not otherwise invalidated, those patents expire between 2027 and 2036.

PROCYSBI received marketing authorization in September 2013 from the EC for marketing in the European Union, or EU. PROCYSBI received ten years of market exclusivity, through 2023, as an orphan drug in Europe.

In the United States, PROCYSBI received seven years of market exclusivity, until February 14, 2023 (including pediatric exclusivity extension), for patients two years of age to less than six years of age, and seven years of market exclusivity, until December 22, 2024, for patients one year of age to less than two years of age as an orphan drug. During December 2017, the FDA awarded pediatric exclusivity to PROCYSBI in the United States, which adds an additional six-month exclusivity period to the end of certain orphan exclusivity periods and patent terms covering PROCYSBI. Under our settlement and license agreement with Lupin, Lupin may enter the market on March 31, 2030, or earlier in certain circumstances.

ACTIMMUNE

We have licenses to U.S. patents covering ACTIMMUNE. If not otherwise invalidated, those patents expire in August 2022.

UPLIZNA

We have U.S. and foreign patents and applications and licenses to U.S. and foreign patents and applications covering UPLIZNA. If not otherwise invalidated, those patents expire between 2026 and 2030. We continue to prosecute and pursue patent protection to obtain additional patent coverage on UPLIZNA and its uses. Additionally, we have biologic exclusivity in the United States covering UPLIZNA that will expire in 2032.

QUINSAIR

We have U.S. and foreign patents and patent applications covering QUINSAIR, as well as licenses from PARI Pharma GmbH and Tripex Pharmaceuticals, LLC to U.S. and foreign patents and patent applications covering QUINSAIR. If not otherwise invalidated, those patents expire between 2026 and 2032.

QUINSAIR received ten years of market exclusivity in the EU, beginning with its March 2015 marketing authorization and expiring in March 2025.

PENNSAID 2%

We own U.S. patents and patent applications covering PENNSAID 2%. We also co-own other U.S. patent applications with Mallinckrodt LLC. If not otherwise invalidated, those patents expire between 2027 and 2030. Under our settlement agreements with Amneal Pharmaceuticals, LLC., Teligent, Inc., Perrigo Company plc, Taro Pharmaceuticals Industries Ltd., Aurolife Pharma, LLC, and Lupin, such parties may enter the market on October 17, 2027, or earlier under certain circumstances.

DUEXIS

We have multiple patents and patent applications related to DUEXIS. Unless otherwise invalidated, those patents expire in 2026. On August 4, 2021, Alkem launched its generic version of DUEXIS in the United States, and we now face generic competition with respect to DUEXIS.

RAYOS

We have an exclusive license to U.S. patents and patent applications from Vectura covering RAYOS. Under our settlement agreement with Teva, Teva may enter the market on December 23, 2022, or earlier under certain circumstances.

VIMOVO

We have licenses to U.S. patents and patent applications and trademarks covering VIMOVO from Nuvo Pharmaceuticals (Ireland) Designated Activity Company, or Nuvo, and AstraZeneca AB. We co-own other U.S. patents and patent applications with Nuvo. If not otherwise invalidated, those in-licensed patents expire between 2022 and 2031. On February 27, 2020, Dr. Reddy's launched its generic version of VIMOVO in the United States, and we now face generic competition with respect to VIMOVO.

For a description of our legal proceedings related to intellectual property matters, see Note 16 of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K.

Third-Party Coverage and Reimbursement

In both U.S. and foreign markets, our ability to commercialize our medicines successfully depends in significant part on the availability of coverage and adequate reimbursement to healthcare providers from third-party payers, including, in the United States, government payers such as the Medicare and Medicaid programs, managed care organizations and private health insurers. Third-party payers are increasingly challenging the prices charged for medicines and examining their cost effectiveness, in addition to their safety and efficacy. This is especially true in markets where over-the-counter and generic options exist. Even if coverage is made available by a third-party payer, the reimbursement rates paid for covered medicines might not be adequate. For example, third-party payers may use tiered coverage and may adversely affect demand for our medicines by not covering our medicines or by placing them in a more expensive formulary tier relative to competitive medicines (where patients have to pay relatively more out of pocket than for medicines in a lower tier). We cannot be certain that our medicines will be covered by third-party payers or that such coverage, where available, will be adequate, or that our medicines will successfully be placed on the list of drugs covered by particular health plan formularies. Many states in the United States have also created preferred drug lists for use in their Medicaid programs and include drugs on those lists only when the manufacturers agree to pay a supplemental rebate. The industry competition to be included on such formularies and preferred drug lists often leads to downward pricing pressures on pharmaceutical companies. Also, third-party payers may refuse to include a particular branded drug on their formularies or otherwise restrict patient assistance to a branded drug when a less costly generic equivalent or other therapeutic alternative is available. In addition, because each third-party payer individually approves coverage and reimbursement levels, obtaining coverage and adequate reimbursement is a time-consuming and costly process. We may be required to provide scientific and clinical support for the use of any medicine to each third-party payer separately with no assurance that approval would be obtained, and we may need to conduct pharmacoeconomic studies to demonstrate the cost effectiveness of our medicines for formulary coverage and reimbursement. Even with studies, our medicines may be considered less safe, less effective or less cost-effective than competitive medicines, and third-party payers may not provide coverage and adequate reimbursement for our medicines or our medicine candidates. These pricing and reimbursement pressures may create negative perceptions to any medicine price increases, or limit the amount we may be able to increase our medicine prices, which may adversely affect our medicine sales and results of operations. Where coverage and reimbursement are not adequate, physicians may limit how much or under what circumstances they will prescribe or administer such medicines, and patients may decline to purchase them. This, in turn, could affect our ability to successfully commercialize our medicines and impact our profitability, results of operations, financial condition, and future success.

The U.S. market has seen a trend in which retail pharmacies have become increasingly involved in determining which prescriptions will be filled with the requested medicine or a substitute medicine, based on a number of factors, including potentially perceived medicine costs and benefits, as well as payer medicine substitution policies. Many states have in place requirements for prescribers to indicate "dispense as written" on their prescriptions if they do not want pharmacies to make medicine substitutions; these requirements are varied and not consistent across states. We may need to increasingly spend time and resources to ensure the prescriptions written for our medicines are filled as written, where appropriate.

Coverage policies, third-party reimbursement rates and medicine pricing regulation have been subject to significant change, and may change further at any time, particularly given recent political focus on the pharmaceutical industry. Even if favorable coverage and adequate reimbursement status is attained for one or more medicines, less favorable coverage policies and reimbursement rates may be implemented in the future.

Government Regulation

The FDA and comparable regulatory agencies in state and local jurisdictions and in foreign countries impose extensive requirements upon the clinical development, pre-market approval, manufacture, labeling, marketing, promotion, pricing, import, export, storage and distribution of medicines. These agencies and other regulatory agencies regulate R&D activities and the testing, approval, manufacture, quality control, safety, effectiveness, labeling, storage, recordkeeping, advertising and promotion of drugs and biologics. Failure to comply with applicable FDA or foreign regulatory agency requirements may result in warning letters, fines, civil or criminal penalties, additional reporting obligations and/or agency oversight, suspension or delays in clinical development, recall or seizure of medicines, partial or total suspension of production or withdrawal of a medicine from the market.

In the United States, the FDA regulates drug products under the Federal Food, Drug, and Cosmetic Act and its implementing regulations and biologics additionally under the Public Health Service Act. The process required by the FDA before medicine candidates may be marketed in the United States generally involves the following:

- submission to the FDA of an investigational new drug, or IND, which must become effective before human clinical trials may begin and must be updated annually;
- completion of extensive pre-clinical laboratory tests and pre-clinical animal studies, all performed in accordance with the FDA's Good Laboratory Practice, or GLP, regulations;
- performance of adequate and well-controlled human clinical trials to establish the safety and efficacy of the medicine candidate for each proposed indication;
- submission to the FDA of a new drug application, or NDA, or BLA as appropriate, after completion of all pivotal clinical trials to demonstrate the safety, purity and potency of the medicine candidate for the indication for use;
- a determination by the FDA within sixty days of its receipt of an NDA or BLA to file the application for review;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facilities to assess compliance with the FDA's current good manufacturing practices, or cGMPs, regulations for pharmaceuticals; and
- FDA review and approval of an NDA or BLA prior to any commercial marketing or sale of the medicine in the United States.

The results of pre-clinical tests (which include laboratory evaluation as well as GLP studies to evaluate toxicity in animals) for a particular medicine candidate, together with related manufacturing information and analytical data, are submitted as part of an IND to the FDA. The IND automatically becomes effective thirty days after receipt by the FDA, unless the FDA, within the thirty-day time period, raises concerns or questions about the conduct of the proposed clinical trial, including concerns that human research subjects will be exposed to unreasonable health risks. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. IND submissions may not result in FDA authorization to commence a clinical trial. A separate submission to an existing IND must also be made for each successive clinical trial conducted during medicine development. Further, an independent institutional review board, or IRB, for each medical center proposing to conduct the clinical trial must review and approve the plan for any clinical trial before it commences at that center and it must monitor the study until completed. The FDA, the IRB or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk. Clinical testing also must satisfy extensive good clinical practice regulations and regulations for informed consent and privacy of individually identifiable information.

Clinical Trials. For purposes of NDA or BLA submission and approval, clinical trials are typically conducted in the following sequential phases, which may overlap:

- *Phase 1.* Studies are initially conducted in a limited population to test the medicine candidate for safety, dose tolerance, absorption, distribution, metabolism, and excretion, typically in healthy humans, but in some cases in patients.
- *Phase 2.* Studies are generally conducted in a limited patient population to identify possible adverse effects and safety risks, explore the initial efficacy of the medicine for specific targeted indications and to determine dose range or pharmacodynamics. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more expensive Phase 3 clinical trials.

- *Phase 3.* These are commonly referred to as pivotal studies. When Phase 2 evaluations demonstrate that a dose range of the medicine is effective and has an acceptable safety profile, Phase 3 clinical trials are undertaken in large patient populations to further evaluate dosage, provide substantial evidence of clinical efficacy and further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial centers.
- *Phase 4.* The FDA may approve an NDA or BLA for a medicine candidate, but require that the sponsor conduct additional clinical trials to further assess the medicine after approval under a post-marketing commitment or post-marketing requirement. In addition, a sponsor may decide to conduct additional clinical trials after the FDA has approved a medicine. Post-approval trials are typically referred to as Phase 4 clinical trials.

The results of drug development, pre-clinical studies and clinical trials are submitted to the FDA as part of an NDA or BLA, as appropriate. Applications also must contain extensive chemistry, manufacturing and control information. Applications must be accompanied by a significant user fee. Once the submission has been accepted for filing, the FDA's goal is to review applications within twelve months of submission or, if the application relates to an unmet medical need in a serious or life-threatening indication, eight months from submission. The review process is often significantly extended by FDA requests for additional information or clarification. The FDA will typically conduct a pre-approval inspection of the manufacturer to ensure that the medicine can be reliably produced in compliance with cGMPs and will typically inspect certain clinical trial sites for compliance with good clinical practice, or GCP. The FDA may refer the application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it typically follows such recommendations. The FDA may deny approval of an application by issuing a Complete Response Letter if the applicable regulatory criteria are not satisfied. A Complete Response Letter may require additional clinical data and/or trial(s), and/or other significant, expensive and time-consuming requirements related to clinical trials, pre-clinical studies or manufacturing. Data from clinical trials are not always conclusive and the FDA may interpret data differently than we or our collaborators interpret data. Approval may occur with boxed warnings on medicine labeling or Risk Evaluation and Mitigation Strategies, or REMS, which limit the labeling, distribution or promotion of a medicine. Once issued, the FDA may withdraw medicine approval if ongoing regulatory requirements are not met or if safety problems occur after the medicine reaches the market. In addition, the FDA may require testing, including Phase 4 clinical trials, and surveillance programs to monitor the safety effects of approved medicines which have been commercialized and the FDA has the power to prevent or limit further marketing of a medicine based on the results of these post-marketing programs or other information.

Clinical Trials in the EU. Clinical trials of medicinal products in the EU must be conducted in accordance with EU and national regulations and the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, or ICH, guidelines on GCP. Additional GCP guidelines from the EC, focusing in particular on traceability, apply to clinical trials of advanced therapy medicinal products. The sponsor must take out a clinical trial insurance policy, and in most EU countries, the sponsor is liable to provide "no fault" compensation to any study subject injured in the clinical trial.

Prior to commencing a clinical trial, the sponsor must obtain a clinical trial authorization from the competent authority, and a positive opinion from an independent ethics committee. The application for a clinical trial authorization must include, among other things, a copy of the trial protocol and an investigational medicinal product dossier containing information about the manufacture and quality of the medicinal product under investigation. Currently, clinical trial authorization applications must be submitted to the competent authority in each EU Member State in which the trial will be conducted. Under the new Clinical Trials Regulation, which came into application on January 31, 2022, there is a centralized application procedure for submitting clinical trial information in the EU, called the Clinical Trial Information System, or CTIS. The EMA will make information stored in CTIS publicly available unless exempted under the Clinical Trial Regulation. The new Clinical Trials Regulation creates greater harmonization of the rules governing the conduct of clinical trials across EU Member States. In all cases, clinical trials must be conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki. Medicines used in clinical trials must be manufactured in accordance with cGMP.

During the development of a medicinal product, the EMA and national medicines regulators within the EU provide the opportunity for dialogue and guidance on the development program. At the EMA level, this is usually done in the form of scientific advice, which is given by the Scientific Advice Working Party of the Committee for Medicinal Products for Human Use. A fee is incurred with each scientific advice procedure. Advice from the EMA is typically provided based on questions concerning, for example, quality (chemistry, manufacturing and controls testing), nonclinical testing and clinical studies, and pharmacovigilance plans and risk-management programs.

Orphan Medicines. Under the Orphan Drug Act, the FDA may designate a medicine as an “orphan drug” if it is intended to treat a rare disease or condition, meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a medicine available in the United States for treatment of the disease or condition will be recovered from sales of the medicine. A company must request orphan drug designation before submitting an NDA for the drug and rare disease or condition. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan drug designation does not shorten the Prescription Drug User Fee Act, or PDUFA, goal dates for the regulatory review and approval process, although it does convey certain advantages such as tax benefits and exemption from the PDUFA application fee.

If a medicine with orphan designation receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the medicine generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor’s marketing application for the same drug for the same indication for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different drug for the same rare disease or condition, nor does it block the approval of the same drug for different indications. If a drug designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity. Orphan exclusivity will not bar approval of another medicine under certain circumstances, including if a subsequent medicine with the same drug for the same indication is shown to be clinically superior to the approved medicine on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand.

In the EU, Regulation (EC) No 141/2000 and Regulation (EC) No. 847/2000 provide that a medicine can be designated as an orphan medicinal product by the EC if its sponsor can establish: that the medicine is intended for the diagnosis, prevention or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the EU when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that the marketing of the medicinal product in the EU would generate sufficient return to justify the necessary investment. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the EU or, if such method exists, the medicinal product will be of significant benefit to those affected by that condition. Once authorized, orphan medicinal products are entitled to ten years of market exclusivity in all EU Member States (extendable to twelve years for medicines that have complied with an agreed pediatric investigation plan pursuant to Regulation 1901/2006) and in addition a range of other benefits during the development and regulatory review process including scientific assistance for study protocols, authorization through the centralized marketing authorization procedure covering all member countries and a reduction or elimination of registration and marketing authorization fees. However, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the regulatory exclusivity period with the consent of the marketing authorization holder for the original orphan medicinal product 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 this medicine is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if, at the end of the fifth year, it can be demonstrated on the basis of available evidence that the criteria for its designation as an orphan medicine are no longer satisfied, for example if the original orphan medicinal product has become sufficiently profitable not to justify maintenance of market exclusivity.

Orphan designation in Great Britain following Brexit is largely aligned with the position in the EU, but is based on the prevalence of the condition in Great Britain (for further details on the impact the United Kingdom, or UK, leaving the EU has and will have, see the section entitled ‘The Impact of Brexit’ below).

Other Regulatory Requirements. Medicines manufactured or distributed pursuant to FDA approvals are subject to continuing regulation by the FDA, including recordkeeping, annual medicine quality review, payment of program fees and reporting requirements. Adverse event experience with the medicine must be reported to the FDA in a timely fashion and pharmacovigilance programs to proactively look for these adverse events are mandated by the FDA. Our medicines may be subject to REMS requirements that affect labeling, distribution or post market reporting. Drug manufacturers and their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMPs, which impose certain procedural and documentation requirements upon us and our third-party manufacturers. Following such inspections, the FDA may issue notices on Form 483 and untitled letters or warning letters that could cause us or our third-party manufacturers to modify certain activities. A Form 483 notice, if issued at the conclusion of an FDA inspection, can list conditions the FDA investigators believe may have violated cGMP or other FDA regulations or guidelines. In addition to Form 483 notices and untitled letters, failure to comply with the statutory and regulatory requirements can subject a manufacturer to possible legal or regulatory action, such as suspension of manufacturing, seizure of medicine, injunctive action, additional reporting requirements and/or oversight by the agency, import alert or possible civil penalties. The FDA may also require us to recall a drug from distribution or withdraw approval for that medicine.

The FDA closely regulates the post-approval marketing and promotion of pharmaceuticals, including standards and regulations for direct-to-consumer advertising, dissemination of off-label information, industry-sponsored scientific and educational activities and promotional activities involving the Internet, including certain social media activities. Medicines may be marketed only for the approved indications and in accordance with the provisions of the approved label. Further, if there are any modifications to the medicine, including changes in indications, labeling, or manufacturing processes or facilities, we may be required to submit and obtain FDA approval of a new or supplemental application, which may require us to develop additional data or conduct additional pre-clinical studies and clinical trials. Failure to comply with these requirements can result in adverse publicity, untitled letters, corrective advertising and potential administrative, civil and criminal penalties, as well as damages, fines, withdrawal of regulatory approval, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs, additional reporting requirements and/or oversight by the agency, and imprisonment, any of which could adversely affect our ability to sell our medicines or operate our business and also adversely affect our financial results.

Physicians may, in their independent medical judgment, prescribe legally available pharmaceuticals for uses that are not described in the medicine's labeling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across certain medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, impose stringent restrictions on manufacturers' communications regarding off-label use. Additionally, a significant number of pharmaceutical companies have been the target of inquiries and investigations by various U.S. federal and state regulatory, investigative, prosecutorial and administrative entities in connection with the promotion of medicines for off-label uses and other sales practices. These investigations have alleged violations of various U.S. federal and state laws and regulations, including claims asserting antitrust violations, violations of the Food, Drug and Cosmetic Act, false claims laws, the Prescription Drug Marketing Act, or PDMA, anti-kickback laws, and other alleged violations in connection with the promotion of medicines for unapproved uses, pricing and Medicare and/or Medicaid reimbursement. If our promotional activities, including any promotional activities that a contracted sales force may perform on our behalf, fail to comply with these regulations or guidelines, we may be subject to warnings from, or enforcement action by, these authorities. In addition, our failure to follow FDA rules and guidelines relating to promotion and advertising may cause the FDA to issue warning letters or untitled letters, suspend or withdraw an approved medicine from the market, require corrective advertising or a recall or result in the imposition of fines or civil fines, additional reporting requirements and/or oversight or could result in disgorgement of money, operating restrictions, injunctions or criminal prosecution by the FDA or other U.S. regulatory agencies, any of which could harm our business. In addition, the distribution of prescription medicines is subject to the PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription medicine samples and impose requirements to ensure accountability in distribution, including a drug pedigree which tracks the distribution of prescription drugs. Further, under the Drug Quality and Security Act, drug manufacturers are subject to a number of requirements, including, medicine identification, tracing and verification, among others, that are designed to detect and remove counterfeit, stolen, contaminated or otherwise potentially harmful drugs from the U.S. drug supply chain.

Outside the United States, the ability of our partners and us to market a medicine is contingent upon obtaining marketing authorization from the appropriate regulatory authorities. The requirements governing marketing authorization, pricing and reimbursement vary widely from country to country and region to region.

The EU and the EEA consist, at the time of writing, of the twenty-seven Member States of the EU (for details on the impact the UK leaving the EU has and will have, see the section entitled “The Impact of Brexit” below), plus Norway, Iceland and Liechtenstein which are Member States of the EEA. These Member States have all acceded to the single market rules governing the supervision of medicinal products. Under the prevailing rules, medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are three procedures for an MA to be obtained:

- the Centralized MA, which is issued by the EC through the Centralized Procedure, based on the scientific opinion of the Committee for Medicinal Products for Human Use of the EMA, and which is valid throughout the entire territory of the EU/EEA. The Centralized Procedure is mandatory for certain types of products, such as (i) biotechnology medicinal products such as genetic engineering, (ii) orphan medicinal products, (iii) medicinal products containing a new active substance indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune and viral diseases and (iv) advanced-therapy medicines, such as gene therapy, somatic cell therapy or tissue-engineered medicines. The Centralized Procedure is optional for products containing a new active substance not authorized in the EU/EEA prior to May 20, 2004, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU.
- Decentralized Procedure MAs are available for products not falling within the mandatory scope of the Centralized Procedure. An identical dossier is submitted to the competent authorities of each of the Member States in which the MA is sought, one of which is selected by the applicant as the Reference Member State, or RMS, to lead the evaluation of the regulatory submission. The competent authority of the RMS prepares a draft assessment report, a draft summary of the product characteristics, or SmPC, and a draft of the labeling and package leaflet as distilled from the preliminary evaluation, which are sent to the other Member States (referred to as the Concerned Member States) for their approval. If the Concerned Member States raise no objections, based on a potential serious risk to public health, to the assessment, SmPC, labeling, or packaging proposed by the RMS, the RMS records the agreement, closes the procedure and informs the applicant accordingly. Each Member State concerned by the procedure is required to adopt a national decision to grant a national MA in conformity with the approved assessment report, SmPC and the labeling and package leaflet as approved. Where a product has already been authorized for marketing in a Member State of the EEA, the granted national MA can be used for mutual recognition in other Member States through the Mutual Recognition Procedure resulting in progressive national approval of the product in the EU/EEA.
- National MAs, which are issued by a single competent authority of the Member States of the EEA and only covers their respective territory, are also available for products not falling within the mandatory scope of the Centralized Procedure. Once a product has been authorized for marketing in a Member State of the EEA through the National Procedure, this National MA can also be recognized in other Member States through the Mutual Recognition Procedure.

Under the procedures described above, before granting the MA, the EMA or the competent authority(ies) of the Member State(s) of the EEA prepare an assessment of the risk-benefit balance of the product against the scientific criteria concerning its quality, safety and efficacy.

Under Regulation (EC) No 726/2004/EC and Directive 2001/83/EC (each as amended), the EU has adopted a harmonized approach to data and market protection or exclusivity (known as the 8 + 2 + 1 formula). The data exclusivity period begins to run on the date when the first MA is granted in the EU. It confers on the MA holder of the reference medicinal product eight years of data exclusivity and ten years of market exclusivity. A reference medicinal product is defined to mean a medicinal product authorized based on a full dossier consisting of pharmaceutical and pre-clinical testing results and clinical trial data, such as a medicinal product containing a new active substance. The ten-year market protection can be extended cumulatively to a maximum period of eleven years if during the first eight years of those ten years of protection period, the MA holder obtains an authorization for one or more new therapeutic indications that are deemed to bring a significant clinical benefit compared to existing therapies.

The exclusivity period means that an applicant for a generic medicinal product is not permitted to rely on pre-clinical pharmacological, toxicological, and clinical data contained in the file of the reference medicinal product of the originator until the first eight years of data exclusivity have expired. Thereafter, a generic product application may be submitted and generic companies may rely on the pre-clinical and clinical data relating to the reference medicinal product to support approval of the generic product. However, a generic product cannot be placed on the market until ten years have elapsed from the initial authorization of the reference medicinal product or eleven years if the protection period is extended, based on the formula of 8+2+1.

In addition to the above, where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity may be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication. Finally, where a change of classification of a medicinal product has been authorized on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorization for a change of classification of the same substance for one year after the initial change was authorized.

The 8 + 2 + 1 exclusivity scheme applies to products that have been authorized in the EU by the EC through the Centralized Procedure or the competent authorities of the Member States of the EEA nationally, including through the Decentralized and Mutual Recognition procedures.

For a medicinal product which has received orphan designation under Regulation 141/2000, it will, as set out in further detail in the section entitled ‘Orphan Medicines’ above, benefit from a period of ten years of orphan market exclusivity which essentially constitutes a period of market monopoly. During this period of orphan market exclusivity, no EU regulatory authority is permitted to accept or approve an application for marketing authorization for a similar medicinal product or an extension application for the same therapeutic indication. This period can be extended cumulatively to a total of twelve years if the marketing authorization holder or applicant complies with the requirements for an agreed pediatric investigation plan pursuant to Regulation 1901/2006.

The holder of a Centralized MA or National MA is subject to various obligations under the applicable EU laws, such as pharmacovigilance obligations, requiring it to, among other things, report and maintain detailed records of adverse reactions, and to submit periodic safety update reports, or PSURs, to the competent authorities. All new marketing authorization applications must include a risk management plan, or RMP, describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product. The regulatory authorities may also impose specific obligations as a condition of the marketing authorization. Such risk-minimization measures or post-authorization obligations may include additional safety monitoring, more frequent submission of PSURs, or the conduct of additional clinical trials or post-authorization safety studies. RMPs and PSURs are routinely available to third parties requesting access, subject to limited redactions. All advertising and promotional activities for the product must be consistent with the approved summary of product characteristics, and therefore all off-label promotion is prohibited. Direct-to-consumer advertising of prescription medicines is also prohibited in the EU. The holder must also ensure that the manufacturing and batch release of its product is in compliance with the applicable requirements. The MA holder is further obligated to ensure that the advertising and promotion of its products complies with applicable EU laws and industry code of practice as implemented in the domestic laws of the Member States of the EU/EEA. The advertising and promotional rules are enforced nationally by the EU/EEA Member States.

The Impact of Brexit. The withdrawal of the UK from the EU (commonly referred to as “Brexit”) took effect on January 31, 2020. Pursuant to the formal withdrawal arrangements agreed between the UK and the EU, the UK was subject to a transition period that ended December 31, 2020, during which EU rules continued to apply. A Trade and Cooperation Agreement, or the TCA, that outlines the trading relationship between the UK and the EU was agreed in December 2020, entered into force provisionally on January 1, 2021, and has been permanently applicable since May 1, 2021. Since a significant portion of the regulatory framework in the UK applicable to our business and our products is derived from EU directives and regulations, Brexit has materially impacted the regulatory regime in the UK with respect to the development, manufacture, importation, approval and commercialization of our products. The regulatory changes that are a result of Brexit may also materially impact upon the development, manufacture, importation, approval and commercialization of our products in the EU, should any development or manufacture of these products take place in the UK.

Great Britain is no longer covered by the EU’s procedures for the grant of marketing authorizations (Northern Ireland will be covered by the centralized authorization procedure and can be covered under the decentralized or mutual recognition procedures). A separate marketing authorization is required to market drugs in Great Britain. However, for two years from January 1, 2021, the UK’s regulator, the Medicines and Healthcare products Regulatory Agency, or MHRA, may adopt decisions taken by the EC on the approval of new marketing authorizations through the centralized procedure, and the MHRA will have regard to marketing authorizations approved in a country in the EEA (although in both cases a marketing authorization will only be granted if any Great Britain-specific requirements are met). Various national procedures are now available to place a drug on the market in the UK, Great Britain, or Northern Ireland, with the main national procedure having a maximum timeframe of 150 days (excluding time taken to provide any further information or data required).

The data exclusivity periods in the UK are currently in line with those in the EU, but the TCA provides that the periods for both data and market exclusivity are to be determined by domestic law, and so there could be divergence in the future.

Orphan designation in Great Britain is based on the prevalence of the condition in Great Britain rather than the EU. It is therefore possible that conditions that are designated as orphan conditions in the EU will not qualify for orphan designation in Great Britain, and that conditions that qualify as an orphan condition in the EU will be designated as such in Great Britain.

Healthcare Fraud and Abuse Laws. As a pharmaceutical company, certain federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to our business. We may be subject to various federal and state laws targeting fraud and abuse in the healthcare industry. For example, in the United States, there are federal and state anti-kickback laws that prohibit the payment or receipt of kickbacks, bribes or other remuneration intended to induce the purchase or recommendation of healthcare products and services or reward past purchases or recommendations. Violations of these laws can lead to significant administrative, civil and criminal penalties, including fines, imprisonment, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement, and exclusion from participation in federal healthcare programs. These laws are applicable to manufacturers of products regulated by the FDA, such as us, and pharmacies, hospitals, physicians and other potential purchasers of such products.

The federal Anti-Kickback Statute prohibits persons and entities from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce either the referral of an individual, or the furnishing, recommending, or arranging for a good or service, for which payment may be made under a federal healthcare program, such as the Medicare and Medicaid programs. The term "remuneration" is defined as any remuneration, direct or indirect, overt or covert, in cash or in kind, and has been broadly interpreted to include anything of value, including for example, gifts, discounts, the furnishing of supplies or equipment, credit arrangements, payments of cash, waivers of payment, ownership interests and providing anything at less than its fair market value. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute may have been violated, and enforcement will depend on the relevant facts and circumstances. The Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA, among other things, amended the intent requirement of the federal Anti-Kickback Statute to state that a person or entity need not have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the ACA provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act (discussed below) or the civil monetary penalties statute, which imposes penalties against any person who is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent, or to have offered improper inducements to federal health care program beneficiaries to select a particular provider or supplier. The federal Anti-Kickback Statute is broad, and despite a series of narrow safe harbors, prohibits many arrangements and practices that are lawful in businesses outside of the healthcare industry. Many states have also adopted laws similar to the federal Anti-Kickback Statute, some of which apply to the referral of patients for healthcare items or services reimbursed by any source, not only the Medicare and Medicaid programs, and do not contain identical safe harbors. In addition, where such activities involve foreign government officials, they may also potentially be subject to the Foreign Corrupt Practices Act. Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities, including our activities with physician customers, pharmacies, and patients, as well as our activities pursuant to partnerships with other companies and pursuant to contracts with contract research organizations, could be subject to challenge under one or more of such laws.

The federal False Claims Act prohibits any person or entity from knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. A claim includes “any request or demand” for money or property presented to the U.S. government. In addition, the ACA specified that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act. The False Claims Act has been the basis for numerous enforcement actions and settlements by pharmaceutical and other healthcare companies in connection with various alleged financial relationships with customers. In addition, a number of pharmaceutical manufacturers have reached substantial financial settlements in connection with allegedly causing false claims to be submitted because of the companies’ marketing of products for unapproved, and thus non-reimbursable, uses. Certain marketing practices, including off-label promotion, may also violate false claims laws, as well as physician self-referral laws, such as the Stark Law, which prohibit a physician from making a referral to certain designated health services with which the physician or the physician’s family member has a financial interest and prohibit submission of a claim for reimbursement pursuant to the prohibited referral. The “qui tam” provisions of the False Claims Act allow a private individual to bring civil actions on behalf of the federal government alleging that the defendant has submitted a false claim to the federal government, and to share in any monetary recovery. In addition, various states have enacted similar fraud and abuse statutes or regulations, including, without limitation, false claims laws analogous to the False Claims Act, and laws analogous to the federal Anti-Kickback Statute, that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer, and there are also federal criminal false claims laws.

Separately, there are a number of other fraud and abuse laws that pharmaceutical manufacturers must be mindful of, particularly after a medicine candidate has been approved for marketing in the United States. For example, a federal criminal law enacted as part of, the Health Insurance Portability and Accountability Act of 1996, or HIPAA, prohibits, among other things, knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payers. The false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. There are also federal civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payers that are false or fraudulent, as well as federal and state consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

We are also subject to analogous foreign laws of each of the above federal healthcare laws and foreign jurisdictions may require the implementation of compliance programs, disclosure of any gifts, compensation, or other remuneration provided to health professionals.

Privacy and Security Laws. We may be subject to, or our marketing activities may be limited by, HIPAA, as amended by the Health Information Technology and Clinical Health Act (HITECH) and their respective implementing regulations, which established uniform standards for certain “covered entities” (covered healthcare providers, health plans and healthcare clearinghouses) governing the conduct of certain electronic healthcare transactions and protecting the security and privacy of protected health information. Among other things, HIPAA’s privacy and security standards are directly applicable to “business associates” — independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity as well as their covered subcontractors. In addition to possible civil and criminal penalties for violations, state attorneys general are authorized to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek attorney’s fees and costs associated with pursuing federal civil actions. Accordingly, state attorneys general (along with private plaintiffs) have brought civil actions seeking injunctions and damages resulting from alleged violations of HIPAA’s privacy and security rules. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

In the EU/EEA, the General Data Protection Regulation (2016/679), or GDPR, went into effect in 2018 and applies to identified or identifiable personal data processed by automated means (for example, a computer database of customers) and data contained in, or intended to be part of, non-automated filing systems (traditional paper files) as well as transfer of such data to a country outside of the EU/EEA. Under the GDPR, fines of up to €20.0 million or up to 4% of the annual global turnover of the infringer, whichever is greater, could be imposed for significant non-compliance. The GDPR includes more stringent operational requirements for processors and controllers of personal data and creates additional rights for data subjects. Further, on July 16, 2020, Europe's top court, the Court of Justice of the EU, ruled in Schrems II (C-311/18) that the Privacy Shield, used by thousands of companies to transfer data between the EU and United States and upon which we relied, was invalid and could no longer be used. In light of Schrems II, organizations may make use of alternative data transfer mechanisms such as the standard contractual clauses approved by the EC, or the SCCs. On June 4, 2021, the EC adopted new SCCs under the GDPR for personal data transfers outside the EEA.

The UK's vote in favor of exiting the EU, often referred to as Brexit, and ongoing developments in the UK have created uncertainty with regard to data protection regulation in the UK. As of January 1, 2021, and the expiry of transitional arrangements agreed to between the UK and EU, data processing in the UK is governed by a UK version of the GDPR (combining the GDPR and the Data Protection Act 2018), exposing us to two parallel regimes, each of which potentially authorizes similar fines and other potentially divergent enforcement actions for certain violations. On June 28, 2021, the EC announced a decision of "adequacy" concluding that the UK ensures an equivalent level of data protection to the GDPR, which removes the need for any additional transfer mechanism to be implemented at present. Some uncertainty remains, however, as this adequacy determination must be renewed after four years and may be modified or revoked in the interim. We cannot fully predict how the Data Protection Act, the UK GDPR, and other UK data protection laws or regulations may develop in the medium to longer term nor the effects of divergent laws and guidance regarding how data transfers to and from the UK will be regulated.

Additionally, the California Consumer Privacy Act, or CCPA, became effective on January 1, 2020. The CCPA has been dubbed the first "GDPR-like" law in the United States since it creates new individual privacy rights for consumers (as that word is broadly defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households (including health information). The CCPA requires covered companies to provide new disclosures to California consumers, provide such consumers new ways to opt-out of certain sales of personal information, and allows for a new cause of action for data breaches. Further, California voters approved a new privacy law, the California Privacy Rights Act, or CPRA, in the November 3, 2020 election. Effective starting on January 1, 2023, the CPRA will significantly modify the CCPA, including by expanding consumers' rights with respect to certain sensitive personal information. The CPRA also creates a new state agency that will be vested with authority to implement and enforce the CCPA and the CPRA. New legislation proposed or enacted in various other states will continue to shape the data privacy environment nationally. For example, on March 2, 2021, Virginia enacted the Virginia Consumer Data Protection Act, which becomes effective on January 1, 2023, and on June 8, 2021, Colorado enacted the Colorado Privacy Act, which takes effect on July 1, 2023.

"Sunshine" and Marketing Disclosure Laws. There are an increasing number of federal and state "sunshine" laws that require pharmaceutical manufacturers to make reports to states on pricing and marketing information. Several states have enacted legislation requiring pharmaceutical companies to, among other things, establish marketing compliance programs, file periodic reports with the state, and make periodic public disclosures on sales and marketing activities, and prohibiting certain other sales and marketing practices. In addition, a similar federal requirement requires certain manufacturers, including pharmaceutical manufacturers, to track and report to the federal government the following: certain payments and other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), certain other healthcare providers (including, for example, physician assistants and nurse practitioners), and teaching hospitals and ownership or investment interests held by physicians and their immediate family members. Certain states, such as Massachusetts, also make the reported information publicly available. In addition, there are state and local laws that require pharmaceutical representatives to be licensed and comply with codes of conduct, transparency reporting, and other obligations. These laws may adversely affect our sales, marketing, and other activities with respect to our medicines in the United States by imposing administrative and compliance burdens on us. If we fail to track and report as required by these laws or otherwise comply with these laws, we could be subject to the penalty provisions of the pertinent state and federal authorities. In the EU/EEA, declaration of transfers of value to healthcare professionals is subject to the requirements under the voluntary industry code of practice. France however has a statutory regime similar to the U.S. Sunshine Act.

Government Price Reporting. For those marketed medicines which are covered in the United States by the Medicaid programs, we have various obligations, including government price reporting and rebate requirements, which generally require medicines be offered at substantial rebates/discounts to Medicaid and certain purchasers (including “covered entities” purchasing under the 340B Drug Discount Program). We are also required to discount such medicines to authorized users of the Federal Supply Schedule of the General Services Administration, under which additional laws and requirements apply. These programs require submission of pricing data and calculation of discounts and rebates pursuant to complex statutory formulas, as well as the entry into government procurement contracts governed by the Federal Acquisition Regulations, and the guidance governing such calculations is not always clear. Compliance with such requirements can require significant investment in personnel, systems and resources, but failure to properly calculate our prices, or offer required discounts or rebates could subject us to substantial penalties. One component of the rebate and discount calculations under the Medicaid and 340B programs, respectively, is the “additional rebate”, a complex calculation which is based, in part, on the extent that a branded drug’s price increases over time more than the rate of inflation (based on the Consumer Price Index for All Urban Consumers). This comparison is based on the baseline pricing data for the first full quarter of sales associated with a branded drug’s NDA, and baseline data cannot generally be reset, even on transfer of the NDA to another manufacturer. This “additional rebate” calculation can, in some cases where price increases have been relatively high versus the first quarter of sales of the NDA, result in Medicaid rebates up to 100 percent of a drug’s “average manufacturer price” and 340B prices of one penny. Governments influence the price of medicinal products in the EU through their pricing and reimbursement rules and control of national healthcare systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies. Other EU Member States allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on healthcare costs in general, particularly prescription medicines, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products.

Penalties. Because of the breadth of these laws and the narrowness of available statutory and regulatory exemptions, it is possible that some of our business activities in the United States could be subject to challenge under one or more of such laws. Moreover, state governmental agencies may propose or enact laws and regulations that extend or contradict federal requirements. If we or our operations are found to be in violation of any of the state or federal laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including significant administrative, civil and criminal penalties, damages, fines, imprisonment, exclusion from participation in U.S. federal or state healthcare programs, additional reporting requirements and/or oversight and the curtailment or restructuring of our operations. To the extent that any medicine we make is sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals. Any penalties, damages, fines, curtailment or restructuring of our operations could materially adversely affect our ability to operate our business and our financial results. We maintain a comprehensive healthcare corporate compliance program. Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, these risks and risks of regulatory non-compliance cannot be entirely eliminated. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management’s attention from the operation of our business. Moreover, achieving and sustaining compliance with applicable federal, state and foreign privacy, security, sunshine, government price reporting, and fraud laws may prove costly.

Impact of Healthcare Reform and Recent Public Scrutiny of Drug Pricing on Coverage, Reimbursement, and Pricing. In the United States and other potentially significant markets for our medicines, federal and state lawmakers and regulatory authorities as well as third-party payers are increasingly attempting to regulate the price of medical products and services, particularly for new and innovative medicines and therapies, which has resulted in delays of coverage decisions, barriers for product access including higher patient copays and in certain cases, leads to lower average net selling prices. Further, there is increased scrutiny of prescription drug pricing practices by federal and state lawmakers and enforcement authorities. In addition, there is an emphasis on managed healthcare in the United States and on country-specific and regional pricing and reimbursement controls in the EU, both of which will put additional pressure on medicine pricing, reimbursement and usage, which may adversely affect our future medicine sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical reimbursement policies and pricing in general.

The U.S. and some foreign jurisdictions are considering or have enacted a number of additional legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our medicines profitably. Among policy makers and payers in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs (including a number of proposals pertaining to prescription drugs, specifically), improving quality and/or expanding access. In the United States, some of the additional proposals to reduce the cost of prescription drug prices considered at the federal level include directing Medicare to negotiate directly with manufacturers for the costliest drugs; various Medicare Part D and Medicaid reforms; price reporting transparency; importation rulemaking; as well as a proposal requiring manufacturers to pay a rebate to the federal government if the price of a Medicare Part B or Part D drug increases more than the rate of inflation.

Also at the federal level, the Trump administration used several means to propose or implement drug pricing reform, including through federal budget proposals, executive orders and policy initiatives. For example, on July 24, 2020, the Trump administration announced several executive orders related to prescription drug pricing that seek to implement several of the administration's proposals. Further, on August 6, 2020, the Trump administration issued another executive order that instructed the federal government to develop a list of "essential" medicines and then buy them and other medical supplies from U.S. manufacturers instead of from companies around the world. The order was meant to reduce regulatory barriers to domestic pharmaceutical manufacturing and catalyze manufacturing technologies needed to keep drug prices low and the production of drug products in the United States. The FDA issued the list of "essential" medicines pursuant to this order on October 30, 2020. As a result of the Trump administration's executive orders, the FDA concurrently released a final rule and guidance in September 2020 providing pathways for states to build and submit importation plans for drugs from Canada. Several states have acted to implement importation plans or have introduced legislation to do so. Further, on November 20, 2020, HHS finalized the "rebate rule" regulation by removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also created a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which have also been delayed until January 1, 2023.

Further, in November 2020, CMS issued an interim final rule implementing the Most Favored Nation, or MFN, Model under which Medicare Part B reimbursement rates for the top fifty drugs covered by Part B will be based on the lowest price drug manufacturers receive in Organization for Economic Cooperation and Development countries with a similar gross domestic product per capita. The MFN Model regulations mandate participation for providers prescribing drugs included on the list and will apply in all U.S. states and territories for a seven-year period that was scheduled to begin on January 1, 2021 and end on December 31, 2027. On December 28, 2020, the United States District Court in Northern California issued a nationwide preliminary injunction against implementation of the interim final rule. As a result of litigation challenging the MFN Model, the interim final rule was formally rescinded on December 27, 2021. The FDA also finalized guidance for manufacturers to obtain an additional National Drug Code for an FDA-approved drug as part of a process to provide a manufacturer a means to import its drugs that were originally intended to be marketed in and authorized for sale in a foreign country. In addition, Congress is continuing to seek new legislative and/or administrative measures to control drug costs.

Further, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024. Finally, Congress is considering health reform measures, including those relating to drug pricing, as part of legislation to implement the Biden Administration's Build Back Better initiative. This legislation is using the budget reconciliation process which requires a majority vote to pass the House and Senate. At present, this legislation has yet to receive a vote in the Senate. This legislation allows Medicare to negotiate the price of drugs that have been on the market for a certain number of years utilizing the non-federal average manufacturer price for high-cost drugs reimbursed by both Medicare Part D and B, but excludes certain orphan drugs from these negotiations. The legislation also contains a perspective inflation rebate, requiring manufacturers who increase their prices faster than inflation to pay a rebate to CMS. The legislation also redesigns the Part D program.

The Biden administration is also continuing efforts to implement drug pricing reform. For example, in July 2021, the administration released an executive order, “Promoting Competition in the American Economy,” with multiple provisions aimed at prescription drugs. In the order, the President directed the Federal Trade Commission to ban “pay for delay” patent settlement agreements, and to identify and address any efforts that impede generic or biosimilar competition. The executive order also directed the FDA to continue to work with states and Indian Tribes to develop importation programs in accordance with Section 804 of the FDCA and FDA regulations. The order directed HHS to increase support for generic and biosimilar drugs by improving standards for the interchangeability of biologic products, supporting biosimilar adoption by increasing education, and facilitating the approval of biosimilars by updating and clarifying existing requirements and procedures related to biologics licensing. Finally, the executive order directs HHS to submit a report detailing a comprehensive plan within 45 days to fight high prescription drug prices and reduce the amount that the federal government pays for drugs. In response to President Biden’s executive order, on September 9, 2021, HHS released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform. These principles are government drug price negotiations, promoting increased competition including changes to supply chains and promoting biosimilars and generics and supporting public and private research. The plan sets out a variety of potential legislative policies that Congress could pursue as well as potential administrative actions HHS can take to advance these principles. No legislation or administrative actions have been finalized to implement the principles.

At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine which drugs, biological products and suppliers will be included in their healthcare programs.

Furthermore, there has been increased interest by third-party payers and governmental authorities in reference pricing systems and publication of discounts and list prices. There also has been particular and increasing legislative and enforcement interest in the United States with respect to relatively large price increases over relatively short time periods. There have been several recent state and federal lawmaker inquiries, proposed legislation and enacted legislation as was the case in California designed to, among other things, bring more transparency to drug pricing, by requiring drug companies to notify insurers and government regulators of price increases and provide an explanation of the reasons for the increase. There have also been actions to review the relationship between pricing and manufacturer patient assistance programs, and reform government program reimbursement methodologies for drugs. Further, a growing number of states have implemented, or are contemplating implementing, drug affordability boards to establish “allowable rates” for certain high-cost drugs identified by such boards.

In addition to the aforementioned price reform measures, there are other potential reform measures relating to the pharmaceutical industry that may impact our business.

In the United States, the pharmaceutical industry has already been significantly affected by major legislative initiatives, including, for example, the ACA. The ACA, among other things, imposes a significant annual fee on companies that manufacture or import branded prescription drug products. It also contains substantial provisions intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, and impose additional health policy reforms, any or all of which may affect our business. There were efforts by the Trump administration as well as judicial and Congressional challenges to numerous provisions of the ACA. For example, on June 17, 2021 the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the ACA is unconstitutional in its entirety because the “individual mandate” was repealed by Congress. Thus, the ACA will remain in effect in its current form. Further, prior to the U.S. Supreme Court ruling, on January 28, 2021, President Biden issued an executive order that initiated a special enrollment period from February 15, 2021 through August 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is possible that the ACA will be subject to judicial or Congressional challenges in the future. It is unclear how any such challenges and the healthcare reform measures of the Biden administration will impact the ACA’s many different provisions affecting the health system, the pharmaceutical sector and our business. We continue to evaluate the effect that such challenges and measures would have on our business. Other legislative changes have also been proposed and adopted since the ACA was enacted. For example, the Budget Control Act of 2011 resulted in aggregate reductions in Medicare payments to providers of up to 2 percent per fiscal year, starting in 2013, and due to subsequent legislative amendments to the statute will remain in effect through 2031, unless additional Congressional action is taken. However, COVID-19 relief legislation suspended the 2% Medicare sequester from May 1, 2020 through March 31, 2022. Under current legislation the actual reduction in Medicare payments will vary from 1% in 2022 to up to 3% in the final fiscal year of this sequester. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Such laws, and others that may affect our business that have been enacted or may in the future be enacted, may result in additional reductions in Medicare and other healthcare funding. In the future, there will likely continue to be additional proposals relating to the reform of the U.S. healthcare system, some of which could further limit coverage and reimbursement of medicines, including our medicine candidates. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payers. Further, the Bipartisan Budget Act of 2018, among other things, amended the ACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans (also known as the Medicare “Donut Hole”), and also increased in 2019 the percentage that a drug manufacturer must discount the cost of prescription drugs from 50 percent to 70 percent. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our medicines.

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 imposed specifically 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 EU. 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. The Criminal Justice (Terrorist Offences) Act 2005 (as amended) also gives the Minister of Finance of Ireland the power to take various measures, including the freezing or seizure of assets, in order to combat terrorism. At present the Financial Transfers Act 1992, certain EU regulations (as implemented into Irish law) and the Criminal Justice (Terrorist Offences) Act 2005 (as amended) prohibit financial transfers involving certain persons and entities associated with the ISIL (Da'esh) and Al-Qaida organizations, the late Slobodan Milosevic and associated persons, Republic of Guinea-Bissau, Myanmar/Burma, 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, South Sudan, Sudan, Somalia, Republic of Guinea, Afghanistan, Egypt, Eritrea, Libya, Syria, Tunisia, Burundi, the Central African Republic, Ukraine, Yemen, Bosnia and Herzegovina, certain known terrorists and terrorist groups, and countries that harbor certain terrorist groups, without the prior permission of the Central Bank of Ireland or the Minister of Finance (as applicable).

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 or EU 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

Withholding 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, or DWT, at the rate of 25 percent, unless an exemption applies.

Dividends on our ordinary shares that are owned by residents of the United States and held beneficially through the Depositary Trust Company, or DTC, will not be subject to DWT provided that the address of the beneficial owner of the ordinary shares in the records of the broker is in the United States.

Dividends on our ordinary shares that are owned by residents of the United States and held directly (outside of DTC) will not be subject to DWT provided that the shareholder has completed the appropriate Irish DWT form and this form remains valid or provides a Certification of U.S. Tax Residency, or Form IRS 6166. Such shareholders must provide the appropriate Irish DWT form or Form IRS 6166 to our transfer agent at least seven business days before the record date for the first dividend payment to which they are entitled.

If any shareholder who is resident in the United States receives a dividend subject to DWT, he or she should generally be able to make an application for a refund from the Irish Revenue Commissioners on the prescribed form (DWT Claim Form 1).

While the U.S./Ireland Double Tax Treaty contains provisions regarding withholding tax, due to the wide scope of the exemptions from DWT available under Irish domestic law, it would generally be unnecessary for a U.S. resident shareholder to rely on the treaty provisions.

Income Tax on Dividends. A shareholder who is neither resident nor ordinarily resident in Ireland and who is entitled to an exemption from DWT generally has no additional liability to Irish income tax or to the universal social charge on a dividend from us.

A shareholder who is neither resident nor ordinarily resident in Ireland and who is not entitled to an exemption from DWT generally has no additional liability to Irish income tax or to the universal social charge on a dividend from us. The DWT deducted by us discharges the liability to Irish income tax and to the universal social charge.

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 percent 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 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 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 percent 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 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 being contemplated.

Employees and Human Capital

As of December 31, 2021, we had approximately 1,890 full-time employees. Of our employees as of December 31, 2021, approximately 500 were engaged in development, regulatory and manufacturing activities, approximately 1,020 were engaged in sales and marketing and approximately 370 were engaged in administration, including business development, finance, legal, information systems, facilities and human resources. None of our employees are subject to a collective bargaining agreement. We consider our employee relations to be good. We are committed to strict policies and procedures to maintain a safe work environment. The health and safety of our employees, customers and communities are of primary concern.

Our human capital resource objectives include identifying, recruiting, retaining, incentivizing and integrating our existing and future employees. In addition to competitive base salaries, the other competitive benefits that we provide to all employees include annual equity and cash incentive plans, retirement benefits and an employee share purchase plan. The principal purposes of these benefits are to attract, retain and reward employees and also, through the granting of share-based and cash-based compensation awards, to secure and retain the services of our employees and provide long-term incentives that align the interests of employees with the interests of our shareholders.

To help us measure and enhance our employees' overall engagement and satisfaction with working at Horizon and to determine areas for improvement, we continuously seek their feedback and suggestions through periodic pulse surveys. In 2021, we conducted multiple surveys to gain feedback on key topics such as well-being, growth and development, manager effectiveness and employee engagement. Participation in the surveys is high, with rates typically averaging above 90% for our annual surveys – and the results, based on sentiment indication, generally exceed top-quartile industry benchmarks. The favorable results indicate to us that our employees are highly motivated to go above and beyond, that they are highly engaged and that they intend to remain at Horizon, an important consideration given the highly competitive nature of our industry. We attribute some of the successful results of our surveys to the fact that we act on much of the feedback we receive from our employees.

Our Core Values

Our culture is reflected in our three core values: growth, accountability and transparency. Through these core values, our teams of highly engaged employees work to better the lives of patients and the community. This engagement is fostered by our strong emphasis on creating a diverse and inclusive culture that drives how we treat employees and expect employees to treat one another.

Growth: We are a high-growth organization that values innovation, development and evolution. We are fiercely innovating to better our communities, our patients and our employees and place a strong emphasis on personal and professional growth. Employees have access to resources to develop their teams and themselves.

Accountability: We strive to do what's right for patients and employees through quality decisions and owning successes and failures. Employees hold each other accountable to make quality decisions that keep our company moving forward to meet the needs of patients.

Transparency: We value the collaboration that is made possible by employees trusting each other to tackle tough challenges and difficult conversations. We are courageous in our decision making, knowing it's necessary to drive our business forward.

We continuously strive to maintain an engaged workforce that is ready to serve patients and health care providers. To that end, employee development is central to how we improve every day. All our employees are encouraged to participate in "Growing Your Career at Horizon," a series of learning events focused on providing guidance around leadership development. Recently – and to support continuous improvement on key culture initiatives – these events have focused on such topics as "inclusive conversations," "strategic mindset" and "managing ambiguity." Additionally, all our employees have unlimited and seamless access to myriad online learning resources. These resources are valuable tools that empower employees to further their professional development while contributing to the growth of our company.

As employees progress in their careers, additional opportunities become available to them, including robust programs intended to grow early career professionals, people managers and future enterprise leaders.

Our Continued Commitment to Employees During the COVID-19 Pandemic

Our commitment to our employees has been exemplified during the COVID-19 crisis. At the onset of the pandemic, in addition to working to support patients, physicians and our communities, we took steps to ensure the health, safety and welfare of our employees, including:

- Implementing travel restrictions and fostering a flexible work environment;
- Implementing a COVID-19 leave policy with 100 percent pay continuation for U.S. employees affected by the virus or needing to care for a family member with the virus, and paid leave for medical professional employees who wished to assist with pandemic-related efforts; and
- Making no furloughs or lay-offs as a result of the pandemic.

Focus on Employee Benefits

At the center of our employee experience is how we reward our employees for the impact they create. We absorb most of the costs for employee medical insurance plans. In addition to medical insurance, we offer a wide variety of benefits that support working families. This includes our parental and caregiver programs. As part of these programs, all caregivers have flexible paid options to care for the needs of their families. These benefits are paid at 100 percent salary. For employees pursuing adoption or surrogacy as a path to parenthood, we offer competitive reimbursement for costs associated with the legal adoption of a child or expenses incurred when using a surrogate.

We offer all full-time employees a “Make it Personal” account, which provides \$500 annually for certain employee personal expenses including student loan repayment, contributions to college savings plans, donations to charitable organizations, health club memberships or purchases of personal health equipment or home office equipment. In addition, all employees have access to an annual “Make it Personal” day. This is an additional 8 hours of paid time off that employees can use to participate in something meaningful or personal to them – from volunteering at a local charity to spending time caring for a loved one.

We also offer competitive educational benefits for our employees and families. We value and encourage continued growth and development of our employees and their families. To support educational goals, we offer several programs to help offset the financial burden of college expenses, including tuition reimbursement, an executive scholarship award for graduate school and scholarships for dependents of our employees.

Our Commitment to Inclusion and Diversity

We are committed to maintaining a workplace free of discrimination, harassment, intimidation or inappropriate conduct based on sex/gender, race, color, religion, national origin, age, disability, veteran status, sexual orientation and/or any other category protected by law. We also provide equal opportunity in employment to all employees and applicants. Equal opportunity rights are applicable to recruitment, hiring, employment and employment-related decisions. In 2020, we introduced RiSE, a strategic program to further embed inclusion, diversity, equity and allyship into the organization. Through RiSE, over 20 volunteer employee leaders work together, leading nine diverse working groups, to enhance and promote our approach to diverse recruitment, professional development, community involvement and building the overall organizational inclusive culture.

Our commitment to inclusion, diversity, equity and allyship is evidenced from the top down. Our CEO, Timothy P. Walbert, was one of the first signatories to the CEO Action for Diversity & Inclusion pledge. Our top leaders have gone through in-depth assessments to determine their inclusive leadership capabilities, with coaching available for leaders who want to enhance their skillset.

We continue to demonstrate gender and ethnicity pay equity, according to a second study conducted in 2021 by a leading third-party compensation consulting firm. The study was a follow-on study to a 2019 study that found no pay discrepancy among men, women and those of different ethnic backgrounds. Both studies analyzed employee demographic and pay data and showed that we provide equal pay for equal work, regardless of gender or ethnicity. We maintained our gender and ethnicity pay equity after our significant growth in the two years since the first study, as well as having completed the acquisition of Viela, which included the addition of a significant number of employees. In addition, our percentage of female employees is over 50 percent and above industry standards.

We continue to receive multiple workplace recognitions, which we believe is evidence of our commitment to employee engagement. In 2021, we received 15 well-known published workplace rankings, two more than in 2020, including four diversity-related workplace awards:

- Crain’s Chicago Business “Best Place to Work in Chicago” (#32) – the sixth consecutive year to be named to the list
- Chicago Tribune’s Top Workplaces (#5) – the seventh consecutive year to be named to the list
- Dave Thomas Foundation for Adoption “Best Adoption-Friendly Workplaces” (#54) – the third consecutive year to be named to the list
- FORTUNE Best Workplaces for Millennials™ (#16) – the second consecutive year to be named to the list
- FORTUNE Best Workplaces for Women™ (#36)
- FORTUNE 100 Best Companies to Work For® (#43)
- FORTUNE Best Workplaces in Health Care & Biopharma™ (#1) – the fifth consecutive year to be named to the list
- Great Place to Work’s Best Workplaces Ireland – Best Small (#12) – the second consecutive year to be named to the list
- Great Place to Work’s Best Workplaces in Chicago™ (#13) – the fifth consecutive year to be named to the list
- Great Place to Work’s Best Workplaces in Texas™ (#8)
- Great Place to Work’s Best Workplaces for Parents™ – the third consecutive year to be named to the list
- PEOPLE Companies that Care® (#82)
- Newsweek’s Most Loved Workplaces (#1)
- San Francisco Bay Area’s Best and Brightest Companies to Work For (Elite Winner – Small Business “Best of the Best”) – the second consecutive year to be named to the list
- The Best and Brightest Companies to Work for in the Nation – the second consecutive year to be named to the list

Available Information

We make available free of charge on or through our internet website our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and all amendments to those reports as soon as reasonably practicable after such material is electronically filed with or furnished to the Securities and Exchange Commission. We also regularly post copies of our press releases as well as copies of presentations and other updates about our business on our website. Our website address is www.horizontherapeutics.com. The information contained in or that can be accessed through our website is not part of this Annual Report on Form 10-K. Information is also available through the Securities and Exchange Commission’s website at www.sec.gov.

Item 1A. Risk Factors

Certain factors may have a material adverse effect on our business, financial condition and results of operations, and you should carefully consider them. Accordingly, in evaluating our business, we encourage you to consider the following discussion of risk factors in its entirety, in addition to other information contained in this report as well as our other public filings with the Securities and Exchange Commission, or SEC.

Risks Related to Our Business and Industry

The COVID-19 global pandemic may continue to adversely impact our business, including the commercialization of our medicines, our supply chain, our clinical trials, our liquidity and access to capital markets and our business development activities.

On March 11, 2020, the World Health Organization made the assessment that a novel strain of coronavirus, which causes the COVID-19 disease, was a pandemic. The President of the United States declared the COVID-19 pandemic a national emergency and many states and municipalities in the United States took aggressive actions to reduce the spread of the disease, including limiting non-essential gatherings of people, ceasing all non-essential travel, ordering certain businesses and government agencies to cease non-essential operations at physical locations and issuing “shelter-in-place” orders which direct individuals to shelter at their places of residence (subject to limited exceptions). Similarly, the Irish government has limited gatherings of people and encouraged employees to work from their homes, and may implement more aggressive policies in the future. Vaccines and treatments have enabled a resumption to more normal business practices and initiatives in many countries, including the United States and Ireland. Restrictions in response to COVID-19, including new variants of the virus, may continue to fluctuate in U.S. states and other geographies and we cannot guarantee that additional U.S. states that have previously reduced restrictions will not reimplement them or that other states will reduce restrictions in the near-term. The effects of government actions and our policies and those of third parties to reduce the spread of COVID-19 may negatively impact productivity and our ability to market and sell our medicines, cause disruptions to our supply chain and ongoing and future clinical trials and impair our ability to execute our business development strategy. These and other disruptions in our operations and the global economy could negatively impact our business, operating results and financial condition.

The commercialization of our medicines has been and may continue to be adversely impacted by COVID-19 and actions taken to slow its spread. For example, patients have postponed visits to healthcare provider facilities, certain healthcare providers have temporarily closed their offices or are restricting patient visits, healthcare provider employees may become generally unavailable and there could be disruptions in the operations of payers, distributors, logistics providers and other third parties that are necessary for our medicines to be prescribed, reimbursed and administered to patients. In addition, due to reduced willingness of patients to visit physician offices and infusion centers, sales of KRYSTEXXA have been negatively impacted, and this impact may continue in future quarters until healthcare activities and patient visits return to normal levels. In addition, during 2021, the impact from COVID-19 and the TEPEZZA supply disruption slowed the generation of TEPEZZA patient enrollment forms, which drive new patient starts. It is also possible that a prolonged period of “shelter-in-place” orders and social distancing behaviors and the associated reduction of physician office visits could force various healthcare practices to permanently close or to consolidate with larger practices or healthcare groups, which could cause us to lose previously-established physician relationships. We cannot predict how long the COVID-19 pandemic will continue to negatively impact sales of our medicines and we expect that even after government-mandated restrictions are lifted, our sales force activities, healthcare provider operations and patients’ willingness to visit healthcare facilities will continue to be limited. We also cannot predict how effective any of our virtual patient, physician and partner support initiatives will be with respect to marketing and supporting the administration and reimbursement of our medicines.

Quarantines, shelter-in-place and similar government orders, or the perception that such orders, shutdowns or other restrictions on the conduct of business operations could occur, related to COVID-19 or other infectious diseases could impact personnel at third-party manufacturing facilities upon which we rely, or the availability or cost of materials, which could disrupt the supply chain for our medicines. In particular, some of our suppliers of certain materials used in the production of our medicines are located in regions that have been subject to COVID-19-related actions and policies that limit the conduct of normal business operations. To the extent our suppliers and service providers are unable to comply with their obligations under our agreements with them or they are otherwise unable to deliver or are delayed in delivering goods and services to us due to COVID-19, our ability to continue meeting commercial demand for our medicines in the United States or advancing development of our medicine candidates may become impaired. For example, in December 2020, pursuant to the Defense Production Act of 1950, or DPA, Catalent Indiana, LLC, or Catalent, was ordered to prioritize certain COVID-19 vaccine manufacturing, resulting in the cancellation of previously guaranteed and contracted TEPEZZA drug product manufacturing slots in December 2020, which were required to maintain TEPEZZA supply. In March 2021, the U.S. Food and Drug Administration, or FDA, approved a prior approval supplement to the TEPEZZA biologics license application, or BLA (which was previously approved in January 2020), giving us authorization to manufacture more TEPEZZA drug product in a batch resulting in an increased number of vials with each manufacturing slot. We commenced resupply of TEPEZZA to the market in April 2021. However, our ability to continue TEPEZZA supply is dependent on future committed manufacturing slots for TEPEZZA not being cancelled and being run successfully, which could be impacted by additional government-mandated COVID-19 vaccine production orders and other risks associated with our reliance on our third-party manufacturers discussed below. If we were to experience another disruption of TEPEZZA supply, it would have a material adverse effect on our operating results and ability to achieve our financial projections in 2022. Refer to the *Impact of COVID-19* section in Item 1 of Part I, *Business*, of this Annual Report on Form 10-K for further information. At this time, we consider our medicine inventories on hand to be sufficient to meet our commercial requirements.

Our clinical trials may be affected by COVID-19. As described in the *Impact of COVID-19* section in Item 1 of Part I, *Business*, of this Annual Report on Form 10-K, certain clinical trials for TEPEZZA were delayed due to the impact of the TEPEZZA supply disruption at Catalent. In addition, clinical site initiation and patient enrollment may be delayed due to staffing shortages or prioritization of hospital and healthcare resources toward COVID-19. Current or potential patients in our ongoing or planned clinical trials may also choose to not enroll, not participate in follow-up clinical visits or drop out of the trial as a precaution against contracting COVID-19. Further, some patients may not be able or willing to comply with clinical trial protocols if quarantines impede patient movement or interrupt healthcare services. Some clinical sites in the United States have slowed or stopped further enrollment of new patients in clinical trials, denied access to site monitors or otherwise curtailed certain operations. Similarly, our ability to recruit and retain principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19, may be adversely impacted. These events could delay our clinical trials, increase the cost of completing our clinical trials and negatively impact the integrity, reliability or robustness of the data from our clinical trials.

The spread of COVID-19 and actions taken to reduce its spread may also materially affect us economically. As a result of the COVID-19 pandemic and actions taken to slow its spread, the global credit and financial markets have experienced extreme volatility and disruptions, including diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. If the equity and credit markets deteriorate, it may make any additional debt or equity financing more difficult, more costly or more dilutive. While the potential economic impact brought by, and the duration of, COVID-19 may be difficult to assess or predict, there could be a significant disruption of global financial markets, reducing our ability to access capital, which could in the future negatively affect our liquidity and financial position or our business development activities.

COVID-19 continues to rapidly evolve. The extent to which COVID-19 may impact the commercialization of our medicines, our supply chain, our clinical trials, our access to capital and our business development activities, will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the ultimate geographic spread of the pandemic, the duration of the pandemic and the efforts by governments and business to contain it, business closures or business disruptions and the impact on the economy and capital markets.

Our ability to generate revenues from our medicines is subject to attaining significant market acceptance among physicians, patients and healthcare payers.

Our current medicines, and other medicines or medicine candidates that we may develop or acquire, may not attain market acceptance among physicians, patients, healthcare payers or the medical community. Some of our medicines, in particular TEPEZZA and UPLIZNA, have not been on the market for an extended period of time, which subjects us to numerous risks as we attempt to increase our market share. We believe that the degree of market acceptance and our ability to generate revenues from our medicines will depend on a number of factors, including:

- timing of market introduction of our medicines as well as competitive medicines;
- efficacy and safety of our medicines;
- continued projected growth of the markets in which our medicines compete;
- the extent to which physicians diagnose and treat the conditions that our medicines are approved to treat;
- prevalence and severity of any side effects;
- if and when we are able to obtain regulatory approvals for additional indications for our medicines;
- acceptance by patients, physicians and applicable specialists;
- availability of, and ability to maintain, coverage and adequate reimbursement and pricing from government and other third-party payers;
- potential or perceived advantages or disadvantages of our medicines over alternative treatments, including cost of treatment and relative convenience and ease of administration;
- strength of sales, marketing and distribution support;
- the price of our medicines, both in absolute terms and relative to alternative treatments;
- impact of past and limitation of future medicine price increases;
- our ability to maintain a continuous supply of our medicines for commercial sale;
- the effect of current and future healthcare laws;
- the extent and duration of the COVID-19 pandemic, including the extent to which physicians and patients delay visits or writing or filling prescriptions for our medicines and the extent to which operations of healthcare facilities, including infusion centers, are reduced;
- the performance of third-party distribution partners, over which we have limited control; and
- medicine labeling or medicine insert requirements of the FDA, or other regulatory authorities.

With respect to TEPEZZA, sales will depend on market acceptance and adoption by physicians and healthcare payers, as well as the ability and willingness of physicians who do not have in-house infusion capability to refer patients to infusion sites of care. With respect to KRYSTEXXA, our ability to grow sales will be affected by the success of our sales, marketing and clinical strategies, which are intended to expand the patient population and usage of KRYSTEXXA. This includes our marketing efforts in nephrology and our studies designed to improve the response rate to KRYSTEXXA, to evaluate a shorter infusion time, and to evaluate the use of KRYSTEXXA in kidney transplant patients. With respect to RAVICTI, which is approved to treat a very limited patient population, our ability to grow sales will depend in large part on our ability to transition urea cycle disorder, or UCD, patients from BUPHENYL or generic equivalents, which are comparatively much less expensive, to RAVICTI and to educate patients and physicians on the benefits of continuing RAVICTI therapy once initiated. With respect to PROCYSBI, which is also approved to treat a very limited patient population, our ability to grow sales will depend in large part on our ability to transition patients from the first-generation immediate-release cysteamine therapy to PROCYSBI, to identify additional patients with nephropathic cystinosis and to educate patients and physicians on the benefits of continuing therapy once initiated. With respect to ACTIMMUNE, while it is the only FDA-approved treatment for chronic granulomatous disease, or CGD, and severe, malignant osteopetrosis, or SMO, they are very rare conditions and, as a result, our ability to grow ACTIMMUNE sales will depend on our ability to identify additional patients with such conditions and educate patients and physicians on the benefits of continuing treatment once initiated. With respect to UPLIZNA, sales will depend on market acceptance and adoption by physicians and healthcare payers, as well as the ability and willingness of physicians who do not have in-house infusion capability to refer patients to infusion sites of care. With respect to each of PENNSAID 2% w/w, or PENNSAID 2%, and RAYOS, their higher cost compared to the generic or branded forms of their active ingredients alone may limit adoption by physicians, patients and healthcare payers. If our current medicines or any other medicine that we may seek approval for, or acquire, fail to attain market acceptance, we may not be able to generate significant revenue to sustain profitability, which would have a material adverse effect on our business, results of operations, financial condition and prospects (including, possibly, the value of our ordinary shares).

Our future prospects are highly dependent on our ability to successfully develop and execute commercialization strategies for each of our medicines. Failure to do so would adversely impact our financial condition and prospects.

A substantial majority of our resources are focused on the commercialization of our current medicines. Our ability to generate significant medicine revenues and to achieve commercial success in the near-term will initially depend almost entirely on our ability to successfully commercialize these medicines in the United States. With respect to our orphan segment, our commercialization strategy includes efforts to increase awareness of the rare conditions that each medicine is designed to treat, enhancing efforts to identify target patients and in certain cases pursue opportunities for label expansion and more effective use through clinical trials, as well as opportunities for commercialization outside of the United States. Our comprehensive post-launch commercial strategy for TEPEZZA aims to enable more thyroid eye disease, or TED, patients to benefit from TEPEZZA. We are doing this by: (i) facilitating continued TEPEZZA uptake in the treatment of TED through continued promotion of TEPEZZA to treating physicians; (ii) continuing to develop the TED market by increasing physician awareness of the disease severity and the urgency to diagnose and treat it, as well as the benefits of treatment with TEPEZZA; (iii) driving accelerated disease identification and time to treatment through our digital and broadcast marketing campaigns; (iv) enhancing the patient journey with our high-touch, patient-centric model as well as support for the patient and site-of-care referral processes; and (v) pursuing more timely access to TEPEZZA for TED patients. Our strategy with respect to KRYSTEXXA includes existing rheumatology account growth, new rheumatology account growth and accelerating nephrology growth, as well as development efforts to enhance response rates through combination treatment with methotrexate and to shorten the infusion time. With respect to RAVICTI and PROCYSBI, our strategy includes accelerating the transition of patients from first-generation therapies, increasing the diagnosis of the associated rare conditions through patient and physician outreach; and increasing compliance rates. Our strategy with respect to ACTIMMUNE, includes increasing awareness and diagnosis of CGD, driving utilization of ACTIMMUNE prophylaxis in newly-diagnosed CGD patients as recommended in current treatment guidelines, encouraging use of ACTIMMUNE in CGD patients prior to bone marrow transplant and in symptomatic carriers of x-linked CGD and increasing compliance rates overall. With respect to our strategy for UPLIZNA, which leverages the successful strategies we have employed with TEPEZZA and KRYSTEXXA, our aim is to (i) increase physician awareness of the benefits of UPLIZNA for the treatment of neuromyelitis optica spectrum disorder, or NMOSD, and what differentiates UPLIZNA from other medicines by generating additional trial data analyses and clinical evidence; (ii) drive patient initiation and adherence, and cultivate a positive patient experience; and (iii) maximize the potential of UPLIZNA through additional indications and global expansion.

We are focusing a significant portion of our commercial activities and resources on TEPEZZA, and we believe our ability to grow our long-term revenues, and a significant portion of the value of our company, relates to our ability to successfully commercialize TEPEZZA in the United States. As a medicine launched for a disease that had no previously-approved treatments, successful commercialization of TEPEZZA is subject to many risks. There are numerous examples of failures to meet high expectations of market potential, including by pharmaceutical companies with more experience and resources than us. While we have established our commercial team and U.S. sales force, we will need to further train and develop the team in order to continue successfully commercializing TEPEZZA. There are many factors that could cause commercialization of TEPEZZA to be unsuccessful, including a number of factors that are outside our control. Because no medicine has previously been approved by the FDA for the treatment of TED, it is especially difficult to estimate TEPEZZA's market potential or the time it will take to increase patient and physician awareness of TED and change current treatment paradigms. In addition, some physicians that are potential prescribers of TEPEZZA do not have the necessary infusion capabilities to administer the medicine and may not otherwise be able or willing to refer their patients to third-party infusion centers, which may discourage them from treating their patients with TEPEZZA. The commercial success of TEPEZZA depends on the extent to which patients and physicians accept and adopt TEPEZZA as a treatment for TED. For example, if the patient population suffering from TED is smaller than we estimate, if it proves difficult to identify TED patients or educate physicians as to the availability and potential benefits of TEPEZZA, or if physicians are unwilling to prescribe or patients are unwilling to take TEPEZZA, the commercial potential of TEPEZZA will be limited. In addition, the prior disruption in TEPEZZA supply resulted in existing patients stopping therapy and an inability of new patients to initiate therapy. We began resupplying TEPEZZA to the market in April 2021. Our ability to continue TEPEZZA supply could be impacted by additional government-mandated COVID-19 vaccine production orders and other risks associated with our reliance on our third-party manufacturers discussed below. We also have limited information regarding how physicians, patients and payers will respond to the pricing of TEPEZZA. Physicians may not prescribe TEPEZZA and patients may be unwilling to use TEPEZZA if coverage is not provided or reimbursement is inadequate to cover a significant portion of the cost. Thus, significant uncertainty remains regarding the commercial potential of TEPEZZA. If the continued commercialization of TEPEZZA becomes unsuccessful or perceived as disappointing, the price of our ordinary shares could decline significantly and long-term success of the medicine and our company could be harmed.

With respect to PENNSAID 2% and RAYOS, our strategy has included entering into rebate agreements with pharmacy benefit managers, or PBMs, where we believe the rebates and costs justify expanded formulary access for patients and ensuring patient assistance to this medicine when prescribed through our HorizonCares program. However, we cannot guarantee that we will be able to secure additional rebate agreements on commercially reasonable terms, that expected volume growth will sufficiently offset the rebates and fees paid to PBMs or that our existing agreements with PBMs will have the intended impact on formulary access. In addition, as the terms of our existing agreements with PBMs expire, we may not be able to renew the agreements on commercially favorable terms, or at all. For each of our inflammation segment medicines, we expect that our commercial success will depend on our sales and marketing efforts in the United States, reimbursement decisions by commercial payers, the expense we incur through our patient assistance program for fully bought down contracts and the rebates we pay to PBMs, as well as the impact of numerous efforts at federal, state and local levels to further reduce reimbursement and net pricing of inflammation segment medicines.

In addition, our strategy for RAYOS in the United States is to focus on the rheumatology indications approved for RAYOS, including our collaboration with the Alliance for Lupus Research, to study the effect of RAYOS on the fatigue experienced by systemic lupus erythematosus, or SLE, patients.

If any of our commercial strategies are unsuccessful or we fail to successfully modify our strategies over time due to changing market conditions, our ability to increase market share for our medicines, grow revenues and to sustain profitability will be harmed.

We are dependent on wholesale distributors for distribution of our products in the United States and, accordingly, our results of operations could be adversely affected if they encounter financial difficulties.

During the year ended December 31, 2021, four wholesale distributors accounted for substantially all of our sales in the United States. If one of our significant wholesale distributors encounters financial or other difficulties, such distributor may decrease the amount of business that it does with us, and we may be unable to collect all the amounts that the distributor owes on a timely basis or at all, which could negatively impact our business and results of operations.

In order to increase adoption and sales of our medicines, we will need to continue developing our commercial organization as well as recruit and retain qualified sales representatives.

Part of our strategy is to continue to build a biotech company to successfully execute the commercialization of our medicines in the U.S. market, and in selected markets outside the United States where we have commercial rights. We may not be able to successfully commercialize our medicines in the United States or in any other territories where we have commercial rights. In order to commercialize any approved medicines, we must continue to build our sales, marketing, distribution, managerial and other non-technical capabilities. As of December 31, 2021, we had approximately 480 sales representatives in the field, consisting of approximately 280 orphan segment sales representatives and 200 inflammation segment sales representatives. We currently have limited resources compared to some of our competitors, and the continued development of our own commercial organization to market our medicines and any additional medicines we may acquire will be expensive and time-consuming. We also cannot be certain that we will be able to continue to successfully develop this capability.

As we continue to add medicines through development efforts and acquisition transactions and execute on our international expansion initiatives, the members of our sales force may have limited experience promoting certain of our medicines. To the extent we employ an acquired entity's sales forces to promote acquired medicines, we may not be successful in continuing to retain these employees and we otherwise will have limited experience marketing these medicines under our commercial organization. In addition, prior to completing the acquisition of Viela Bio, Inc., or Viela, in March 2021, we had no experience as an organization commercializing UPLIZNA. We are required to expend significant time and resources to train our sales force to be credible and able to educate physicians on the benefits of prescribing and pharmacists dispensing our medicines. In addition, we must train our sales force to ensure that a consistent and appropriate message about our medicines is being delivered to our potential customers. Our sales representatives may also experience challenges promoting multiple medicines when we call on physicians and their office staff. We have experienced, and may continue to experience, turnover of the sales representatives that we hired or will hire, requiring us to train new sales representatives. If we are unable to recruit and retain qualified personnel outside of the United States, we may not be able to execute our global expansion strategy successfully. If we are unable to effectively train our sales force and equip them with effective materials, including medical and sales literature to help them inform and educate physicians about the benefits of our medicines and their proper administration and label indication, as well as our patient assistance programs, our efforts to successfully commercialize our medicines could be put in jeopardy, which could have a material adverse effect on our financial condition, share price and operations.

As a result of the evolving role of various constituents in the prescription decision making process, we focus on hiring sales representatives for our inflammation segment medicines with successful business to business experience. While we believe the profile of our representatives is suited for this environment, we cannot be certain that our representatives will be able to successfully protect our market for PENNSAID 2% and RAYOS or that we will be able to continue attracting and retaining sales representatives with our desired profile and skills. We will also have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train and retain commercial personnel. To the extent we rely on additional third parties to commercialize any approved medicines, we may receive less revenue than if we commercialized these medicines ourselves. In addition, we may have little or no control over the sales efforts of any third parties involved in our commercialization efforts. In the event we are unable to successfully develop and maintain our own commercial organization or collaborate with a third-party sales and marketing organization, we may not be able to commercialize our medicines and medicine candidates and execute on our business plan.

Coverage and reimbursement may not be available, or reimbursement may be available at only limited levels, for our medicines, which could make it difficult for us to sell our medicines profitably.

Market acceptance and sales of our medicines will depend in large part on global coverage and reimbursement policies and may be affected by future healthcare reform measures, both in the United States and other key international markets. Successful commercialization of our medicines will depend in part on the availability of governmental and third-party payer reimbursement for the cost of our medicines. Government health administration authorities, private health insurers and other organizations generally provide reimbursement for healthcare. In particular, in the United States, private health insurers and other third-party payers often provide reimbursement for medicines and services based on the level at which the government (through the Medicare or Medicaid programs) provides reimbursement for such treatments. In the United States, the European Union, or EU, and other significant or potentially significant markets for our medicines and medicine candidates, government authorities and third-party payers are increasingly attempting to limit or regulate the price of medicines and services, particularly for new and innovative medicines and therapies, which has resulted in lower average selling prices. Further, the increased scrutiny of prescription drug pricing practices and emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the EU and other significant or potentially significant markets will put additional pressure on medicine pricing, reimbursement and usage, which may adversely affect our medicine sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical reimbursement policies and pricing in general. These pressures may create negative reactions to any medicine price increases, or limit the amount by which we may be able to increase our medicine prices, which may adversely affect our medicine sales and results of operations.

We expect to experience pricing pressures in connection with the sale of our medicines due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative proposals relating to outcomes and quality. For example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the ACA, increased the mandated Medicaid rebate from 15.1% to 23.1%, expanded the rebate to Medicaid managed care utilization and increased the types of entities eligible for the federal 340B drug discount program. As concerns continue to grow over the need for tighter oversight, there remains the possibility that the Health Resources and Services Administration or another agency under the U.S. Department of Health and Human Services, or HHS, will propose a similar regulation or that Congress will explore changes to the 340B program through legislation. For example, a bill was introduced in 2018 that would require hospitals to report their low-income utilization of the program. Further, the Centers for Medicare & Medicaid Services, or CMS, issued a final rule in 2018 that implemented civil monetary penalties for manufacturers who exceeded the ceiling price methodology for a covered outpatient drug when selling to a 340B covered entity. Pursuant to the final rule, after January 1, 2019, manufacturers must calculate 340B program ceiling prices on a quarterly basis. Moreover, manufacturers could be subject to a \$5,000 penalty for each instance where they knowingly and intentionally overcharge a covered entity under the 340B program. With respect to KRYSTEXXA, the “additional rebate” methodology of the 340B pricing rules, as applied to the historical pricing of KRYSTEXXA both before and after we acquired the medicine, have resulted in a 340B ceiling price of one penny. A material portion of KRYSTEXXA prescriptions (normally in the range of low to mid-teens percent) are written by healthcare providers that are eligible for 340B drug pricing and therefore the reduction in 340B pricing to a penny has negatively impacted our net sales of KRYSTEXXA. The CMS previously revised the Medicare hospital outpatient prospective payment system by creating a new, significantly reduced reimbursement methodology for drugs purchased under the 340B program for Medicare patients at hospital and other settings. These reductions are currently under review by the U.S. Supreme Court and it is unclear how it will rule. A decision is expected in 2022 but, in the meantime, the CMS final rule for calendar year 2022 continues these reductions for drugs acquired through the 340B program.

Patients are unlikely to use our medicines unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our medicines. Third-party payers may limit coverage to specific medicines on an approved list, also known as a formulary, which might not include all of the FDA-approved medicines for a particular indication. Moreover, a third-party payer’s decision to provide coverage for a medicine does not imply that an adequate reimbursement rate will be approved. Additionally, one third-party payer’s decision to cover a particular medicine does not ensure that other payers will also provide coverage for the medicine, or will provide coverage at an adequate reimbursement rate. Even though we have contracts with some PBMs in the United States, that does not guarantee that they will perform in accordance with the contracts, nor does that preclude them from taking adverse actions against us, which could materially adversely affect our operating results. In addition, the existence of such PBM contracts does not guarantee coverage by such PBM’s contracted health plans or adequate reimbursement to their respective providers for our medicines. For example, some PBMs have placed some of our medicines on their exclusion lists from time to time, which has resulted in a loss of coverage for patients whose healthcare plans have adopted these PBM lists. Additional healthcare plan formularies may also exclude our medicines from coverage due to the actions of certain PBMs, future price increases we may implement, our use of the HorizonCares program or other free medicine programs whereby we assist qualified patients with certain out-of-pocket expenditures for our medicine, including donations to patient assistance programs offered by charitable foundations, or any other co-pay programs, or other reasons. If our strategies to mitigate formulary exclusions are not effective, these events may reduce the likelihood that physicians prescribe our medicines and increase the likelihood that prescriptions for our medicines are not filled.

In light of such policies and the uncertainty surrounding proposed regulations and changes in the coverage and reimbursement policies of governments and third-party payers, we cannot be sure that coverage and reimbursement will be available for any of our medicines in any additional markets or for any other medicine candidates that we may develop. Also, we cannot be sure that reimbursement amounts will not reduce the demand for, or the price of, our medicines. If coverage and reimbursement are not available or are available only at limited levels, we may not be able to successfully commercialize our medicines.

There may be additional pressure by payers, healthcare providers, state governments, federal regulators and Congress, to use generic drugs that contain the active ingredients found in our medicines or any other medicine candidates that we may develop or acquire. If we fail to successfully secure and maintain coverage and adequate reimbursement for our medicines or are significantly delayed in doing so, we will have difficulty achieving market acceptance of our medicines and expected revenue and profitability which would have a material adverse effect on our business, results of operations, financial condition and prospects.

We may also experience pressure from payers as well as state and federal government authorities concerning certain promotional approaches that we may implement such as our HorizonCares program or any other co-pay programs. Certain state and federal enforcement authorities and members of Congress have initiated inquiries about co-pay assistance programs. Some state legislatures have implemented or have been considering implementing laws to restrict or ban co-pay coupons for branded drugs. For example, legislation was signed into law in California that would limit the use of co-pay coupons in cases where a lower cost generic drug is available and if individual ingredients in combination therapies are available over the counter at a lower cost. It is possible that similar legislation could be proposed and enacted in additional states. Additionally, numerous organizations, including pharmaceutical manufacturers, have been subject to ongoing litigation, enforcement actions and settlements related to their patient assistance programs and support. If we are unsuccessful with our HorizonCares program or any other co-pay programs, or we alternatively are unable to secure expanded formulary access through additional arrangements with PBMs or other payers, we would be at a competitive disadvantage in terms of pricing versus preferred branded and generic competitors. We may also experience financial pressure in the future which would make it difficult to support investment levels in areas such as managed care contract rebates, HorizonCares and other access tools.

Our medicines are subject to extensive regulation, and we may not obtain additional regulatory approvals for our medicines.

The clinical development, manufacturing, labeling, packaging, storage, recordkeeping, advertising, promotion, export, marketing and distribution and other possible activities relating to our medicines and our medicine candidates are, and will be, subject to extensive regulation by the FDA and other regulatory agencies. Failure to comply with FDA and other applicable regulatory requirements may, either before or after medicine approval, subject us to administrative or judicially imposed sanctions.

To market any drugs or biologics outside of the United States, we and current or future collaborators must comply with numerous and varying regulatory and compliance related requirements of other countries. For example, we are pursuing a global expansion strategy, which includes bringing TEPEZZA to patients with TED outside of the United States. Japan is one of the countries we are pursuing and, in February 2022, we initiated a Phase 3 randomized, placebo-controlled clinical trial for the treatment of moderate-to-severe active TED patients in Japan. Furthermore, in November 2021, we announced that the Committee for Medicinal Products for Human Use of the EMA, adopted a positive opinion recommending grant of a Centralised Marketing Authorisation, or CMA, for UPLIZNA as a monotherapy for the treatment of adult patients with NMOSD who are anti-aquaporin-4 immunoglobulin G seropositive (AQP4-IgG+). While the Committee for Orphan Medicinal Products did not recommend maintenance of the orphan designation for UPLIZNA following its review, we are continuing to invest in our European infrastructure to support a potential European launch of UPLIZNA for NMOSD, which we anticipate would begin with Germany in the second quarter of 2022, assuming the grant of a CMA by the European Commission, or EC. In addition, on March 23, 2021, our strategic partner, Mitsubishi Tanabe Pharma Corporation, or MTPC, received manufacturing and marketing approval of UPLIZNA for NMOSD in Japan. UPLIZNA was launched in Japan during the second quarter of 2021. Approval procedures vary among countries and can involve additional medicine testing and additional administrative review periods, including obtaining reimbursement and pricing approval in select markets. The time required to obtain approval in other countries might differ from that required to obtain FDA approval. The regulatory approval process in other countries may include all of the risks associated with FDA approval as well as additional, presently unanticipated, risks. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others.

Applications for regulatory approval, including a marketing authorization application, or MAA, for marketing new drugs in the European Economic Area (which consists of the Member States of the EU, Iceland, Liechtenstein and Norway), or EEA, must be supported by extensive clinical and pre-clinical data, as well as extensive information regarding chemistry, manufacturing and controls, or CMC, to demonstrate the safety and effectiveness of the applicable medicine candidate. The number and types of pre-clinical studies and clinical trials that will be required for regulatory approval varies depending on the medicine candidate, the disease or the condition that the medicine candidate is designed to target and the regulations applicable to any particular medicine candidate. Despite the time and expense associated with pre-clinical and clinical studies, failure can occur at any stage, and we could encounter problems that cause us to repeat or perform additional pre-clinical studies, CMC studies or clinical trials. Regulatory authorities could delay, limit or deny approval of a medicine candidate for many reasons, including because they:

- may not deem a medicine candidate to be adequately safe and effective;
- may not find the data from pre-clinical studies, CMC studies and clinical trials to be sufficient to support a claim of safety and efficacy;
- may interpret data from pre-clinical studies, CMC studies and clinical trials significantly differently than we do;
- may not approve the manufacturing processes or facilities associated with our medicine candidates;
- may conclude that we have not sufficiently demonstrated long-term stability of the formulation for which we are seeking marketing approval;
- may change approval policies (including with respect to our medicine candidates' class of drugs) or adopt new regulations; or
- may not accept a submission due to, among other reasons, the content or formatting of the submission.

Even if we believe that data collected from our pre-clinical studies, CMC studies and clinical trials of our medicine candidates are promising and that our information and procedures regarding CMC are sufficient, our data may not be sufficient to support marketing approval by regulatory authorities, or regulatory interpretation of these data and procedures may be unfavorable. For example, based upon the results of our MIRROR randomized controlled trial evaluating KRYSTEXXA and methotrexate versus KRYSTEXXA alone, we submitted a supplemental BLA for KRYSTEXXA in the first quarter of 2022, but we cannot guarantee that the FDA will accept our submission for filing or will approve a revised label for KRYSTEXXA. Even if approved, medicine candidates may not be approved for all indications requested and such approval may be subject to limitations on the indicated uses for which the medicine may be marketed, restricted distribution methods or other limitations. Our business and reputation may be harmed by any failure or significant delay in obtaining regulatory approval for the sale of any of our medicine candidates. We cannot predict when or whether regulatory approval will be obtained for any medicine candidate we develop.

The ultimate approval and commercial marketing of any of our medicines in additional indications or geographies is subject to substantial uncertainty. Failure to gain additional regulatory approvals would limit the potential revenues and value of our medicines and could cause our share price to decline.

Since a significant proportion of the regulatory framework in the United Kingdom, or UK, applicable to our business and our products is derived from EU directives and regulations, Brexit has materially impacted the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our products in the UK. The regulatory changes that are a result of Brexit may also materially impact upon the development, manufacture, importation, approval and commercialization of our products in the EEA, should any development or manufacture of these products take place in the UK.

Great Britain is no longer covered by the EU's procedures for the grant of marketing authorizations (Northern Ireland is still covered by the centralized authorization procedure which leads to a marketing authorization that is valid throughout the EEA and can participate, with certain restrictions, in the other procedures available to market a medicine in the EU). 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 UK and/or the 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 UK and/or EEA for our medicine candidates, which could significantly and materially harm our business.

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 UK and EU customs agencies that may delay time-sensitive shipments and may negatively impact our product supply chain.

We are subject to ongoing obligations and continued regulatory review by the FDA and equivalent foreign regulatory agencies, and we may be subject to penalties and litigation and large incremental expenses if we fail to comply with regulatory requirements or experience problems with our medicines.

Our current FDA-approved medicines (and our medicine candidates, if approved) are subject to extensive ongoing obligations and continued regulatory review with respect to many operational aspects including our manufacturing processes, labeling, packaging, distribution, storage, adverse event monitoring and reporting, dispensation, advertising, promotion and recordkeeping. These requirements include submissions of safety and other post-marketing information and reports, ongoing maintenance of medicine registration and continued compliance with current good manufacturing practices, or cGMPs, good clinical practices, or GCPs, International Council for Harmonisation, or ICH, guidelines, good pharmacovigilance practice, good distribution practices and good laboratory practices, or GLPs, which are regulations and guidelines enforced by the FDA for all of our medicines in clinical development and for any clinical trials that we conduct post-approval.

Later discovery of previously unknown problems with a medicine or medicine candidate, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- injunctions or restrictions on the marketing, manufacturing or distribution of the medicine, suspension or withdrawal of medicine approvals, withdrawal of the medicine from the market, revocation of necessary licenses or suspension of medicine reimbursement;
- issuance of warning letters, show cause notices or untitled letters describing alleged violations, which may be publicly available;
- suspension of any ongoing clinical trials or delay or prevention of the initiation of clinical trials;
- delay or refusal to approve pending applications or supplements to approved applications we have filed;
- refusal to permit drugs or precursor or intermediary chemicals to be imported or exported to or from the United States;
- medicine seizure or detention, refusal to permit the import or export of medicines, or voluntary or mandatory medicine recalls;
- suspension, restrictions or additional requirements on operations, including costly new manufacturing quality or pharmacovigilance requirements; and/or
- criminal investigations and prosecutions, injunctions, the imposition of civil or criminal penalties, or exclusion, debarment or suspension from government healthcare programs.

Moreover, existing regulatory approvals and any future regulatory approvals that we obtain will be subject to limitations on the approved indicated uses and patient populations for which our medicines may be marketed, the conditions of approval, requirements for potentially costly, post-market testing, including Phase 4 clinical trials, and requirements for surveillance to monitor the safety and efficacy of the medicines. Physicians nevertheless may prescribe our medicines to their patients in a manner that is inconsistent with the approved label or that is off-label. Positive clinical trial results in any of our medicine development programs increase the risk that approved pharmaceutical forms of the same active pharmaceutical ingredients, or APIs, may be used off-label in those indications. A significant number of pharmaceutical companies have been the target of inquiries and investigations by various U.S. federal and state regulatory, investigative, prosecutorial and administrative entities in connection with the promotion of medicines for off-label uses and other sales practices. These investigations have alleged violations of various U.S. federal and state laws and regulations, including claims asserting antitrust violations, violations of the Food, Drug and Cosmetic Act, or FDCA, anti-kickback laws, and other alleged violations in connection with the promotion of medicines for unapproved uses, pricing and Medicare and/or Medicaid reimbursement. If we are found to have improperly promoted off-label uses of approved medicines, we may be subject to significant sanctions, civil and criminal fines and injunctions prohibiting us from engaging in specified promotional conduct.

In addition, engaging in improper promotion of our medicines for off-label uses in the United States can subject us to false claims litigation under federal and state statutes. These false claims statutes in the United States include the federal False Claims Act, which allows any individual to bring a lawsuit against a pharmaceutical company on behalf of the federal government alleging submission of false or fraudulent claims or causing to present such false or fraudulent claims for payment by a federal program such as Medicare or Medicaid. Growth in false claims litigation has increased the risk that a pharmaceutical company will have to defend a false claim action, pay civil money penalties, settlement fines or restitution, agree to comply with burdensome reporting and compliance obligations and be excluded from Medicare, Medicaid and other federal and state healthcare programs.

The regulations, policies or guidance of regulatory agencies may change and new or additional statutes or government regulations may be enacted that could prevent or delay regulatory approval of our medicine candidates or further restrict or regulate post-approval activities. For example, there remains a substantial amount of uncertainty regarding internet and social media promotion of regulated medical products. We cannot predict the likelihood, nature or extent of adverse government regulation that may arise from pending or future legislation or administrative action, either in the United States or abroad. If we are unable to achieve and maintain regulatory compliance, we will not be permitted to market our drugs, which would materially adversely affect our business, results of operations and financial condition.

We have rights to medicines in certain jurisdictions but have little or no control over third parties that have rights to commercialize those medicines in other jurisdictions, which could adversely affect our commercialization of these medicines.

Following our sale of the rights to RAVICTI outside of North America to Medical Need Europe AB, part of the Immedica Group, or Immedica, Immedica has marketing and distribution rights to RAVICTI in those regions. Following our sale of the rights to PROCYSBI in the Europe, Middle East and Africa, or EMEA, regions to Chiesi Farmaceutici S.p.A., or Chiesi, in June 2017, or the Chiesi divestiture, Chiesi has marketing and distribution rights to PROCYSBI in the EMEA regions. MTPC has rights to the development and commercialization of UPLIZNA for NMOSD as well as other potential future indications in Japan and certain other countries in Asia. Hansoh Pharmaceutical Group Company Limited, or Hansoh, has rights to the development and commercialization of UPLIZNA for NMOSD as well as other potential future indications in China, Hong Kong and Macau. Miravo Healthcare (formerly known as Nuvo Pharmaceuticals Inc.), or Miravo, has retained its rights to PENNSAID 2% in territories outside of the United States. In March 2017, Miravo announced that it had entered into an exclusive license agreement with Sayre Therapeutics PVT Ltd. to distribute, market and sell PENNSAID 2% in India, Sri Lanka, Bangladesh and Nepal, and in December 2017 Miravo announced that it had entered into a license and distribution agreement with Gebro Pharma AG for the exclusive right to register, distribute, market and sell PENNSAID 2% in Switzerland and Liechtenstein. We have little or no control over Immedica's activities with respect to RAVICTI outside of North America, over Chiesi's activities with respect to PROCYSBI in the EMEA, over MTPC's or Hansoh's activities with respect to UPLIZNA in the certain countries in Asia, or over Miravo's or its existing and future commercial partners' activities with respect to PENNSAID 2% outside of the United States even though those activities could impact our ability to successfully commercialize these medicines. For example, Immedica or its assignees, Chiesi or its assignees, MTPC or Hansoh or their respective assignees or Miravo or its assignees can make statements or use promotional materials with respect to RAVICTI, PROCYSBI, UPLIZNA or PENNSAID 2%, respectively, outside of the United States that are inconsistent with our positioning of the medicines in the United States, and could sell RAVICTI, PROCYSBI, UPLIZNA or PENNSAID 2%, respectively, in foreign countries at prices that are dramatically lower than the prices we charge in the United States. These activities and decisions, while occurring outside of the United States, could harm our commercialization strategy in the United States. In addition, medicine recalls or safety issues with these medicines outside the United States, even if not related to the commercial medicine we sell in the United States, could result in serious damage to the brand in the United States and impair our ability to successfully market them. We also rely on Immedica, Chiesi, MTPC, Hansoh and Miravo, or their assignees to provide us with timely and accurate safety information regarding the use of these medicines outside of the United States, as we have or will have limited access to this information ourselves.

We rely on third parties to manufacture commercial supplies of all of our medicines, and we currently intend to rely, in whole or in part, on third parties to manufacture commercial supplies of any other approved medicines. The commercialization of any of our medicines could be stopped, delayed or made less profitable if those third parties fail to provide us with sufficient quantities of medicine or fail to do so at acceptable quality levels or prices or fail to maintain or achieve satisfactory regulatory compliance.

The facilities used by our third-party manufacturers to manufacture our medicines and medicine candidates must be approved by the applicable regulatory authorities. We do not control the manufacturing processes of third-party manufacturers and are currently completely dependent on our third-party manufacturing partners.

We rely on AGC Biologics A/S (formerly known as CMC Biologics A/S), or AGC Biologics, as our exclusive manufacturer of the TEPEZZA drug substance and Catalent and Patheon Pharmaceuticals Inc., or Patheon (contract development and manufacturing organization services of Thermo Fisher Scientific), as our manufacturers for TEPEZZA drug product. In December 2020, pursuant to the DPA, Catalent was ordered to prioritize certain COVID-19 vaccine manufacturing, resulting in the cancellation of previously guaranteed and contracted TEPEZZA drug product manufacturing slots, which were required to maintain TEPEZZA supply. To offset the reduced slots allowed by the DPA and Catalent, we accelerated plans to increase the production scale of TEPEZZA drug product. In March 2021, the FDA approved a prior approval supplement to the TEPEZZA BLA (which was previously approved in January 2020), giving us authorization to manufacture more TEPEZZA drug product in a batch resulting in an increased number of vials with each manufacturing slot. We commenced resupply of TEPEZZA to the market in April 2021, but we cannot guarantee that our future contracted TEPEZZA manufacturing slots at Catalent will not be rescheduled or canceled as a result of additional U.S. government-mandated COVID-19 vaccine production orders. In December 2021, we received FDA approval for our second drug product filling site at Patheon, on lines where COVID-19 products are not filled to ensure more reliable and consistent supply of TEPEZZA. During the third quarter of 2021, we were informed that one of our contract manufacturers for TEPEZZA is manufacturing an adjuvant for a COVID-19 vaccine. The adjuvant is being manufactured on a different line to the line used to manufacture our medicine. We do not expect the manufacturing of this adjuvant to impact the supply of our medicine. While we are not currently aware of any manufacturing facilities, other than Catalent and the other previously mentioned contract manufacturer, that are part of the supply chain for our medicines that are being utilized for the manufacture of vaccines for COVID-19, similar circumstances could arise in the future and could result in supply disruption to our other medicines. Further, following the highly successful launch of TEPEZZA, which significantly exceeded our expectations, we began the process of expanding our production capacity in 2020 to meet anticipated future demand for TEPEZZA. If AGC Biologics fails to supply TEPEZZA drug substance or if Catalent fails to supply TEPEZZA drug product for a period beyond our current expectation or either manufacturer is otherwise unable to meet our volume requirements due to unexpected market demand for TEPEZZA, it may lead to further TEPEZZA supply constraints.

We rely on NOF Corporation, or NOF, as our exclusive supplier of the PEGylation agent that is a critical raw material in the manufacture of KRYSTEXXA. If NOF fails to supply such PEGylation agent, it may lead to KRYSTEXXA supply constraints. A key excipient used in PENNSAID 2% as a penetration enhancer is dimethyl sulfoxide, or DMSO. We and Miravo, our exclusive supplier of PENNSAID 2%, rely on a sole proprietary form of DMSO for which we maintain a substantial safety stock. However, should this supply become inadequate, damaged, destroyed or unusable, we and Miravo may not be able to qualify a second source. We rely on an exclusive supply agreement with Boehringer Ingelheim Biopharmaceuticals GmbH, or Boehringer Ingelheim Biopharmaceuticals, for manufacturing and supply of ACTIMMUNE. ACTIMMUNE is manufactured by starting with cells from working cell bank samples which are derived from a master cell bank. We and Boehringer Ingelheim Biopharmaceuticals separately store multiple vials of the master cell bank. In the event of catastrophic loss at our or Boehringer Ingelheim Biopharmaceuticals' storage facility, it is possible that we could lose multiple cell banks and have the manufacturing capacity of ACTIMMUNE severely impacted by the need to substitute or replace the cell banks. In addition, we rely on AstraZeneca UK Limited for the manufacture of the current clinical and commercial supplies of UPLIZNA, and for the current clinical and nonclinical supplies of the other medicine candidates acquired in the Viela acquisition.

In July 2021, we purchased a biologic drug product manufacturing facility in Waterford, Ireland, which is intended to be an additional source of manufacturing to supplement the capabilities of our third-party drug product manufacturers. We are in the process of completing the build-out and validation of this facility and assuming timely receipt of regulatory approvals, we expect that the first medicine manufactured at the facility to be approved for release in 2023. However, we have no experience as a company in developing, validating, obtaining regulatory approval for or running a manufacturing facility and may not be successful in these activities. Even if we are successful in producing medicines at the Waterford facility for commercial sale once we receive the required regulatory approvals, we expect to remain dependent on our third-party drug product filling manufacturing partners in the near-term and to a lesser extent in the medium/longer term, but we plan to always dual source our strategic products.

If we or any of our third-party manufacturers cannot successfully manufacture material that conforms to our specifications and the applicable regulatory authorities' strict regulatory requirements, or pass regulatory inspection, we or our third-party manufacturers will not be able to secure or maintain regulatory approval for the manufacturing facilities. In addition, we have no direct control over the ability of third-party manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or any other applicable regulatory authorities do not approve these facilities for the manufacture of our medicines or if they withdraw any such approval in the future, or if our suppliers or third-party manufacturers decide they no longer want to supply our primary active ingredients or manufacture our medicines, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our medicines. To the extent our manufacturing facility of that of any third-party manufacturers that we engage with respect to our medicines are different from those currently being used for commercial supply in the United States, the FDA will need to approve such facilities prior to our sale of any medicine using these facilities.

Although we have entered into supply agreements for the manufacture and packaging of our medicines, our manufacturers may not perform as agreed or may terminate their agreements with us. We currently rely on single source suppliers for certain of our medicines. If our manufacturers terminate their agreements with us, we may have to qualify new back-up manufacturers. We rely on safety stock to mitigate the risk of our current suppliers electing to cease producing bulk drug product or ceasing to do so at acceptable prices and quality. However, we can provide no assurance that such safety stocks would be sufficient to avoid supply shortfalls in the event we have to identify and qualify new contract manufacturers.

The manufacture of medicines requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of medicines often encounter difficulties in production, particularly in scaling up and validating initial production. These problems include difficulties with production costs and yields, quality control, including stability of the medicine, quality assurance testing, shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. Furthermore, if microbial, viral or other contaminations are discovered in the medicines or in the manufacturing facilities in which our medicines are made, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination. We cannot assure that issues relating to the manufacture of any of our medicines will not occur in the future. Additionally, we or our third-party manufacturers may experience manufacturing difficulties due to resource constraints or as a result of labor disputes or unstable political environments. If we or our third-party manufacturers were to encounter any of these difficulties, or our third-party manufacturers otherwise fail to comply with their contractual obligations, our ability to commercialize our medicines or provide any medicine candidates to patients in clinical trials would be jeopardized.

Any delay or interruption in our ability to meet commercial demand for our medicines will result in the loss of potential revenues and could adversely affect our ability to gain market acceptance for these medicines. In addition, any delay or interruption in the supply of clinical trial supplies could delay the completion of clinical trials, increase the costs associated with maintaining clinical trial programs and, depending upon the period of delay, require us to commence new clinical trials at additional expense or terminate clinical trials completely.

Failures or difficulties faced at any level of our supply chain, including any further potential disruption caused by the COVID-19 pandemic, could materially adversely affect our business and delay or impede the development and commercialization of any of our medicines or medicine candidates and could have a material adverse effect on our business, results of operations, financial condition and prospects.

We face significant competition from other biotechnology and pharmaceutical companies, including those marketing generic medicines and our operating results will suffer if we fail to compete effectively.

The biotechnology and pharmaceutical industries are intensely competitive. We have competitors both in the United States and international markets, including major multinational pharmaceutical companies, biotechnology companies and universities and other research institutions. Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development, or R&D, staff, experienced marketing and manufacturing organizations and well-established sales forces. Additional consolidations in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors and we will have to find new ways to compete and may have to potentially merge with or acquire other businesses to stay competitive. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or in-licensing on an exclusive basis, medicines that are more effective and/or less costly than our medicines.

Although TEPEZZA does not face direct competition, other therapies, such as corticosteroids, have been used on an off-label basis to alleviate some of the symptoms of TED. While these therapies have not proved effective in treating the underlying disease, and carry with them significant side effects, their off-label use could reduce or delay treatment in the addressable patient population for TEPEZZA. Immunovant Inc., or Immunovant, is conducting Phase 2 clinical trials of a fully human anti-FcRn monoclonal antibody candidate for the treatment of active TED, also referred to as Graves' ophthalmopathy. On February 2, 2021, Immunovant announced a voluntary pause in the clinical dosing of the candidate due to elevated total cholesterol and low-density lipoprotein levels in patients treated with the candidate. Immunovant has indicated it intends to continue developing the candidate but did not provide an estimate of when the dosing might resume. Viridian Therapeutics, Inc. is pursuing development of two anti-IGF-1R monoclonal antibodies for TED and has initiated a Phase 1/2 trial in the fourth quarter of 2021. While KRYSTEXXA faces limited direct competition, a number of competitors have medicines in clinical trials, including Selecta Biosciences Inc., or Selecta, which has initiated a Phase 3 clinical program of a candidate for the treatment of chronic refractory gout. In September 2020, Selecta announced topline clinical data that did not meet the primary endpoint or demonstrate statistical superiority for its Phase 2 trial that compared its candidate, which includes an immunomodulator, to KRYSTEXXA alone. In July 2020, Selecta and Swedish Orphan Biovitrum AB, or Sobi, entered into a strategic licensing agreement under which Sobi will assume responsibility for certain development, regulatory, and commercial activities for this candidate. In December 2021, Selecta and Sobi announced the completion of enrollment for DISSOLVE I, the first of two clinical studies of the Phase 3 DISSOLVE development program of SEL-212 for chronic refractory gout. SEL-212 is a combination of Selecta's ImmTOR immune tolerance platform and a therapeutic uricase enzyme (pegadricase). RAVICTI could face competition from a few alternative medicine and treatment options that are in development, including a gene-therapy candidate by Ultragenyx Pharmaceutical Inc., a generic taste-masked formulation option of sodium phenylbutyrate by ACER Therapeutics Inc., an enzyme replacement for a specific UCD subtype (ARG) by Aeglea Bio Therapeutics Inc. and a mRNA-based therapeutic for a specific UCD subtype (OTC) by Arcturus Therapeutics Holdings Inc. PROCYSBI faces competition from Cystagon® (immediate-release cysteamine bitartrate capsules) for the treatment of cystinosis, Cystadrops® (cysteamine ophthalmic solution) for the treatment of corneal cystine crystal deposits and Cystaran™ (cysteamine ophthalmic solution) for treatment of corneal crystal accumulation in patients with cystinosis. Additionally, we are also aware that AVROBIO, Inc. has a gene therapy candidate in development for the treatment of cystinosis. UPLIZNA faces competition from eculizumab, marketed as Soliris® by AstraZeneca plc, or AstraZeneca, and satralizumab, marketed as Enspryng™ by Chugai Pharmaceuticals Co., Ltd., a subsidiary of F. Hoffmann-La Roche Ltd., each for the treatment of patients with NMOSD. AstraZeneca is also conducting a Phase 3 trial with Ultomiris® (ravulizumab) in NMOSD and, if approved for this indication, UPLIZNA could face additional competition. UPLIZNA also faces competition from rituximab, an off-label treatment that has been used for years to treat NMOSD given the lack of an approved medicine for this disease prior to 2019. PENNSAID 2% faces competition from generic versions of diclofenac sodium topical solutions that are priced significantly less than the price we charge for PENNSAID 2%. The generic version of Voltaren Gel is the market leader in the topical NSAID category. Legislation enacted in most states in the United States allows, or in some instances mandates, that a pharmacist dispense an available generic equivalent when filling a prescription for a branded medicine, in the absence of specific instructions from the prescribing physician. Because pharmacists often have economic and other incentives to prescribe lower-cost generics, if physicians prescribe PENNSAID 2%, those prescriptions may not result in sales. If physicians do not complete prescriptions through our HorizonCares program or otherwise provide prescribing instructions prohibiting generic diclofenac sodium topical solutions as a substitute for PENNSAID 2%, sales of PENNSAID 2% may suffer despite any success we may have in promoting PENNSAID 2% to physicians.

We have also entered into settlement and license agreements that may allow certain of our competitors to sell generic versions of certain of our medicines in the United States, subject to the terms of such agreements. We granted (i) non-exclusive licenses to manufacture and commercialize generic versions of PENNSAID 2% in the United States after October 17, 2027, (ii) a non-exclusive license to manufacture and commercialize a generic version of RAYOS tablets in the United States after December 23, 2022, (iii) non-exclusive licenses to manufacture and commercialize generic versions of RAVICTI in the United States after July 1, 2025 and (iv) non-exclusive license to manufacture and commercialize a generic version of PROCYSBI in the United States after March 31, 2030. Under certain circumstances, each of these licenses could become effective on an earlier date.

On August 4, 2021, following a judgment in the District Court of Delaware, which was subsequently affirmed by the Federal Circuit Court of Appeals on November 16, 2021, Alkem Laboratories, Inc., or Alkem, launched a generic version of DUEXIS in the United States. As a result, we have repositioned our promotional efforts previously directed to DUEXIS to the other inflammation segment medicines and expect that our DUEXIS net sales will continue to decrease in future periods.

ACTIMMUNE is the only medicine currently approved by the FDA specifically for the treatment of CGD and SMO. While there are additional or alternative approaches used to treat patients with CGD and SMO, there are currently no medicines on the market that compete directly with ACTIMMUNE. A widely accepted protocol to treat CGD in the United States is the use of concomitant “triple prophylactic therapy” comprising ACTIMMUNE, an oral antibiotic agent and an oral antifungal agent. However, the FDA-approved labeling for ACTIMMUNE does not discuss this “triple prophylactic therapy,” and physicians may choose to prescribe one or both of the other modalities in the absence of ACTIMMUNE. Because of the immediate and life-threatening nature of SMO, the preferred treatment option for SMO is often to have the patient undergo a bone marrow transplant which, if successful, will likely obviate the need for further use of ACTIMMUNE in that patient. Likewise, the use of bone marrow transplants in the treatment of patients with CGD is becoming more prevalent, which could have a material adverse effect on sales of ACTIMMUNE and its profitability. We are aware of a number of research programs investigating the potential of gene therapy as a possible cure for CGD. Additionally, other companies may be pursuing the development of medicines and treatments that target the same diseases and conditions which ACTIMMUNE is currently approved to treat. As a result, it is possible that our competitors may develop new medicines that manage CGD or SMO more effectively, cost less or possibly even cure CGD or SMO. In addition, the U.S. patents covering ACTIMMUNE expire in August 2022, and although we are not currently aware of any biosimilar to ACTIMMUNE under development, the development and commercialization of any competing medicines or the discovery of any new alternative treatment for CGD or SMO could have a material adverse effect on sales of ACTIMMUNE and its profitability.

BUPHENYL’s composition of matter patent protection and orphan drug exclusivity have expired. Because BUPHENYL has no regulatory exclusivity or listed patents, there is nothing to prevent a competitor from submitting an ANDA for a generic version of BUPHENYL and receiving FDA approval. Generic versions of BUPHENYL to date have been priced at a discount relative to RAVICTI, and physicians, patients, or payers may decide that this less expensive alternative is preferable to RAVICTI. If this occurs, sales of RAVICTI could be materially reduced, but we would nevertheless be required to make royalty payments to Bausch Health Companies Inc. (formerly Ucylyd Pharma, Inc.), or Bausch, and another external party, at the same royalty rates. While Bausch and its affiliates are generally contractually prohibited from developing or commercializing new medicines, anywhere in the world, for the treatment of UCD or hepatic encephalopathy, or HE, which are chemically similar to RAVICTI, they may still develop and commercialize medicines that compete with RAVICTI. For example, medicines approved for indications other than UCD and HE may still compete with RAVICTI if physicians prescribe such medicines off-label for UCD or HE. We are also aware that Recordati S.p.A (formerly known as Orphan Europe SARL), or Recordati, received FDA approval in January 2021 for carglumic acid for the treatment of acute hyperammonemia due to propionic acidemia or methylmalonic acidemia. Carglumic acid, sold under the name Carbaglu, is also approved for chronic and acute hyperammonemia due to N-acetylglutamate synthase deficiency, a rare UCD subtype. RAVICTI may face additional competition from this compound.

The availability and price of our competitors’ medicines could limit the demand, and the price we are able to charge, for our medicines. We will not successfully execute on our business objectives if the market acceptance of our medicines is inhibited by price competition, if physicians are reluctant to switch from existing medicines to our medicines, or if physicians switch to other new medicines or choose to reserve our medicines for use in limited patient populations.

In addition, established pharmaceutical companies may invest heavily to accelerate discovery and development of novel compounds or to acquire novel compounds that could make our medicines obsolete. Our ability to compete successfully with these companies and other potential competitors will depend largely on our ability to leverage our experience in clinical, regulatory and commercial development to:

- develop and acquire medicines that are superior to other medicines in the market;
- attract qualified clinical, regulatory, and sales and marketing personnel;
- obtain patent and/or other proprietary protection for our medicines and technologies;
- obtain required regulatory approvals; and
- successfully collaborate with pharmaceutical companies in the discovery, development and commercialization of new medicine candidates.

Our biologic medicines and candidates may face biosimilar competition sooner than anticipated.

Even if we are successful in achieving regulatory approval to commercialize a biologic medicine candidate ahead of our competitors, our biologic medicines and candidates may face competition from biosimilar products. In the United States, the Biologics Price Competition and Innovation Act of 2009, or BPCIA, created an abbreviated pathway for FDA approval of biosimilar and interchangeable biological products based on a previously licensed reference product. Under the BPCIA, an application for a biosimilar biological product cannot be approved by the FDA until 12 years after the original reference biological product was approved under a BLA. The law is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation, and meaning are subject to uncertainty and any such processes could have a material adverse effect on the future commercial prospects for our biologic medicines and candidates.

We believe that any of our candidates approved as a biological product under a BLA should qualify for the 12-year period of exclusivity available to reference biological products. However, there is a risk that this exclusivity could be shortened due to congressional action or otherwise, or that the FDA will not consider our candidates to be reference biological products pursuant to its interpretation of the exclusivity provisions of the BPCIA for competing products, potentially creating the opportunity for biosimilar competition sooner than anticipated. Moreover, the extent to which a biosimilar product, once approved, will be substituted for any one of our reference medicines in a way that is similar to traditional generic substitution for non-biological products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing including whether a future competitor seeks an interchangeability designation for a biosimilar of one of our medicines. Under the BPCIA as well as state pharmacy laws, only interchangeable biosimilar products are considered substitutable for the reference biological product without the intervention of the health care provider who prescribed the original biological product. However, as with all prescribing decisions made in the context of a patient-provider relationship and a patient's specific medical needs, healthcare providers are not restricted from prescribing biosimilar products in an off-label manner. In addition, a competitor could decide to forego the abbreviated approval pathway available for biosimilar products and to submit a full BLA for product licensure after completing its own preclinical studies and clinical trials. In such a situation, any exclusivity to which we may be eligible under the BPCIA would not prevent the competitor from marketing its biological product as soon as it is approved.

In Europe, the EC has granted marketing authorizations for several biosimilar products pursuant to a set of general and product class-specific guidelines for biosimilar approvals issued over the past few years. In addition, companies may be developing biosimilar products in other countries that could compete with our medicines, if approved.

If competitors are able to obtain marketing approval for biosimilars referencing our medicine candidates, if approved, our future medicines may become subject to competition from such biosimilars, whether or not they are designated as interchangeable, with the attendant competitive pressure and potential adverse consequences. Such competitive products may be able to immediately compete with us in each indication for which our medicine candidates may have received approval.

If we are unable to maintain or realize the benefits of orphan drug exclusivity, we may face increased competition with respect to certain of our medicines.

Under the Orphan Drug Act of 1983, the FDA may designate a medicine as an orphan drug if it is a drug intended to treat a rare disease or condition affecting fewer than 200,000 people in the United States. A company that first obtains FDA approval for a designated orphan drug for the specified rare disease or condition receives orphan drug marketing exclusivity for that drug for a period of seven years from the date of its approval. PROCYSBI received ten years of market exclusivity, through 2023, as an orphan drug in Europe. PROCYSBI received seven years of market exclusivity, until February 14, 2023 (including pediatric exclusivity extension), for patients two years of age to less than six years of age, and seven years of market exclusivity, until December 22, 2024, for patients one year of age to less than two years of age as an orphan drug in the United States. TEPEZZA has been granted orphan drug exclusivity for treatment of active (dynamic) phase Graves' ophthalmopathy, which we expect will provide orphan drug marketing exclusivity in the United States until January 2027. In addition, UPLIZNA was granted orphan drug exclusivity for the treatment of NMOSD, which we expect will provide orphan drug marketing exclusivity in the United States until June 2027. However, despite orphan drug exclusivity, the FDA can still approve another drug containing the same active ingredient and used for the same orphan indication if it determines that a subsequent drug is safer, more effective or makes a major contribution to patient care, and orphan exclusivity can be lost if the orphan drug manufacturer is unable to ensure that a sufficient quantity of the orphan drug is available to meet the needs of patients with the rare disease or condition. Orphan drug exclusivity may also be lost if the FDA later determines that the initial request for designation was materially defective. In addition, orphan drug exclusivity does not prevent the FDA from approving competing drugs for the same or similar indication containing a different active ingredient. If orphan drug exclusivity is lost and we were unable to successfully enforce any remaining patents covering the applicable medicine, we could be subject to generic competition and revenues from the medicine could decrease materially.

In addition, if a subsequent drug is approved for marketing for the same or a similar indication as our medicines despite orphan drug exclusivity, we may face increased competition and lose market share with respect to these medicines.

If we cannot successfully implement our patient assistance programs or increase formulary access and reimbursement for our medicines in the face of increasing pressure to reduce the price of medications, the adoption of our medicines by physicians, patients and payers may decline.

There continues to be immense pressure from healthcare payers, PBMs and others to use less expensive or generic medicines or over-the-counter brands instead of certain branded medicines. For example, some PBMs have placed certain of our medicines on their exclusion lists from time to time, which has resulted in a loss of coverage for patients whose healthcare plans have adopted these PBM lists. Additional healthcare plans, including those that contract with these PBMs but use different formularies, may also choose to exclude our medicines from their formularies or restrict coverage to situations where a generic or over-the-counter medicine has been tried first. Many payers and PBMs also require patients to make co-payments for branded medicines, including many of our medicines, in order to incentivize the use of generic or other lower-priced alternatives instead. Legislation enacted in most states in the United States allows, or in some instances mandates, that a pharmacist dispenses an available generic equivalent when filling a prescription for a branded medicine, in the absence of specific instructions from the prescribing physician. Because our medicines (other than BUPHENYL, DUEXIS and VIMOVO) do not currently have FDA-approved generic equivalents in the United States, we do not believe our medicines should be subject to mandatory generic substitution laws. If limitations in coverage and other incentives result in patients refusing to fill prescriptions or being dissatisfied with the out-of-pocket costs of their medications, or if pharmacies otherwise seek and receive physician authorization to switch prescriptions, not only would we lose sales on prescriptions that are ultimately not filled, but physicians may be dissuaded from writing prescriptions for our medicines in the first place in order to avoid potential patient non-compliance or dissatisfaction over medication costs, or to avoid spending the time and effort of responding to pharmacy requests to switch prescriptions.

Part of our commercial strategy to increase adoption and access to our inflammation medicines in the face of these incentives to use generic alternatives is to offer physicians the opportunity to have eligible patients fill prescriptions through independent pharmacies participating in our HorizonCares patient assistance program, including shipment of prescriptions to patients. We also have contracted with a third-party prescription clearinghouse that offers physicians a single point of contact for processing prescriptions through these independent pharmacies, reducing physician administrative costs, increasing the fill rates for prescriptions and enabling physicians to monitor refill activity. Through HorizonCares, financial assistance may be available to reduce eligible patients' out-of-pocket costs for prescriptions filled. Because of this assistance, eligible patients' out-of-pocket cost for our medicines when dispensed through HorizonCares may be significantly lower than such costs when our medicines are dispensed outside of the HorizonCares program. However, to the extent physicians do not direct prescriptions currently filled through traditional pharmacies, including those associated with or controlled by PBMs, to pharmacies participating in our HorizonCares program, we may experience a significant decline in PENNSAID 2% prescriptions. Our ability to increase utilization of our patient assistance programs will depend on physician and patient awareness and comfort with the programs, and we do not control whether physicians will ultimately use our patient assistance programs to prescribe our medicines or whether patients will agree to receive our medicines through our HorizonCares program. In addition, the HorizonCares program is not available to federal health care program (such as Medicare and Medicaid) beneficiaries. We have also contracted with certain PBMs and other payers to secure formulary status and reimbursement for certain of our inflammation segment medicines, which generally require us to pay administrative fees and rebates to the PBMs and other payers for qualifying prescriptions. While we have business relationships with two of the largest PBMs, Express Scripts, Inc., or Express Scripts, and CVS Caremark, as well as rebate agreements with other PBMs, and we believe these agreements will secure formulary status for certain of our medicines, we cannot guarantee that we will be able to agree to terms with other PBMs and other payers, or that such terms will be commercially reasonable to us. Despite our agreements with PBMs, the extent of formulary status and reimbursement will ultimately depend to a large extent upon individual healthcare plan formulary decisions. If healthcare plans that contract with PBMs with which we have agreements do not adopt formulary changes recommended by the PBMs with respect to our medicines, we may not realize the expected access and reimbursement benefits from these agreements. In addition, we generally pay higher rebates for prescriptions covered under plans that adopt a PBM-chosen formulary than for plans that adopt custom formularies. Consequently, the success of our PBM contracting strategy will depend not only on our ability to expand formulary adoption among healthcare plans, but also upon the relative mix of healthcare plans that have PBM-chosen formularies versus custom formularies. If we are unable to realize the expected benefits of our contractual arrangements with the PBMs we may continue to experience reductions in net sales from our inflammation segment medicines and/or reductions in net pricing for our inflammation segment medicines due to increasing patient assistance costs. If we are unable to increase adoption of HorizonCares for filling prescriptions of our medicines and to secure formulary status and reimbursement through arrangements with PBMs and other payers, particularly with healthcare plans that use custom formularies, our ability to achieve net sales growth for our inflammation segment medicines would be impaired.

There has been negative publicity and inquiries from Congress and enforcement authorities regarding the use of specialty pharmacies and drug pricing. Our patient assistance programs are not involved in the prescribing of medicines and are solely to assist in ensuring that when a physician determines one of our medicines offers a potential clinical benefit to their patients and they prescribe one for an eligible patient, financial assistance may be available to reduce the patient's out-of-pocket costs. In addition, all pharmacies that fill prescriptions for our medicines are fully independent, including those that participate in HorizonCares. We do not own or possess any option to purchase an ownership stake in any pharmacy that distributes our medicines, and our relationship with each pharmacy is non-exclusive and arm's length. All of our sales are processed through pharmacies independent of us. Despite this, the negative publicity and interest from Congress and enforcement authorities regarding specialty pharmacies may result in physicians being less willing to participate in our patient assistance programs and thereby limit our ability to increase patient assistance and adoption of our medicines.

We may also encounter difficulty in forming and maintaining relationships with pharmacies that participate in our patient assistance programs. We currently depend on a limited number of pharmacies participating in HorizonCares to fulfill patient prescriptions under the HorizonCares program. If these HorizonCares participating pharmacies are unable to process and fulfill the volume of patient prescriptions directed to them under the HorizonCares program, our ability to maintain or increase prescriptions for our medicines will be impaired. The commercialization of our medicines and our operating results could be affected should any of the HorizonCares participating pharmacies choose not to continue participation in our HorizonCares program or by any adverse events at any of those HorizonCares participating pharmacies. For example, pharmacies that dispense our medicines could lose contracts that they currently maintain with managed care organizations, or MCOs, including PBMs. Pharmacies often enter into agreements with MCOs. They may be required to abide by certain terms and conditions to maintain access to MCO networks, including terms and conditions that could limit their ability to participate in patient assistance programs like ours. Failure to comply with the terms of their agreements with MCOs could result in a variety of penalties, including termination of their agreement, which could negatively impact the ability of those pharmacies to dispense our medicines and collect reimbursement from MCOs for such medicines.

The HorizonCares program may implicate certain federal and state laws related to, among other things, unlawful schemes to defraud, excessive fees for services, healthcare kickbacks, tortious interference with patient contracts and statutory or common law fraud. We have a comprehensive compliance program in place to address adherence with various laws and regulations relating to the selling, marketing and manufacturing of our medicines, as well as certain third-party relationships, including pharmacies. Specifically, with respect to pharmacies, the compliance program utilizes a variety of methods and tools to monitor and audit pharmacies, including those that participate in the HorizonCares program, to confirm their activities, adjudication and practices are consistent with our compliance policies and guidance. Despite our compliance efforts, to the extent the HorizonCares program is found to be inconsistent with applicable laws or the pharmacies that participate in our patient assistance programs do not comply with applicable laws, we may be required to restructure or discontinue such programs, terminate our relationship with certain pharmacies, or be subject to other significant penalties.

If the cost of maintaining our patient assistance programs increases relative to our sales revenues, we could be forced to reduce the amount of patient financial assistance that we offer or otherwise scale back or eliminate such programs, which could in turn have a negative impact on physicians' willingness to prescribe and patients' willingness to fill prescriptions of our medicines. While we believe that our arrangements with PBMs will result in broader inclusion of certain of our inflammation segment medicines on healthcare plan formularies, and therefore increase payer reimbursement and lower our cost of providing patient assistance programs, these arrangements generally require us to pay administrative and rebate payments to the PBMs and/or other payers and their effectiveness will ultimately depend to a large extent upon individual healthcare plan formulary decisions that are beyond the control of the PBMs. If our arrangements with PBMs and other payers do not result in increased prescriptions and reductions in our costs to provide our patient assistance programs that are sufficient to offset the administrative fees and rebate payments to the PBMs and/or other payers, our financial results may continue to be harmed.

If we are unable to successfully implement our commercial plans and facilitate adoption by patients and physicians of any approved medicines through our sales, marketing and commercialization efforts, then we will not be able to generate sustainable revenues from medicine sales which will have a material adverse effect on our business and prospects.

Our business operations may subject us to numerous commercial disputes, claims and/or lawsuits and such litigation may be costly and time-consuming and could materially and adversely impact our financial position and results of operations.

Operating in the pharmaceutical industry, particularly the commercialization of medicines, involves numerous commercial relationships, complex contractual arrangements, uncertain intellectual property rights, potential product liability and other aspects that create heightened risks of disputes, claims and lawsuits. In particular, we may face claims related to the safety of our medicines, intellectual property matters, employment matters, tax matters, commercial disputes, competition, sales and marketing practices, environmental matters, personal injury, insurance coverage and acquisition or divestiture-related matters. Similarly, from time to time we are involved in disputes with distributors, PBMs and licensing partners regarding our rights and performance of obligations under contractual arrangements. Any commercial dispute, claim or lawsuit may divert management's attention away from our business, we may incur significant expenses in addressing or defending any commercial dispute, claim or lawsuit, and we may be required to pay damage awards or settlements or become subject to equitable remedies that could adversely affect our operations and financial results.

Litigation related to these disputes may be costly and time-consuming and could materially and adversely impact our financial position and results of operations if resolved against us.

A variety of risks associated with operating our business internationally could adversely affect our business.

We have operations in the United States, Ireland and in multiple other jurisdictions, and are pursuing a global expansion strategy, which includes bringing TEPEZZA to patients with TED outside of the United States. Japan is one of the countries we are pursuing and, in February 2022, we initiated a Phase 3 randomized, placebo-controlled clinical trial for the treatment of moderate-to-severe active TED patients in Japan. Furthermore, we are investing in our European infrastructure to support the potential first-half 2022 approval of UPLIZNA by the EMA for NMOSD. We face risks associated with our international operations, including possible unfavorable political, tax and labor conditions, which could harm our business.

We are subject to numerous risks associated with international business activities, including:

- compliance with Irish laws and the maintenance of our Irish tax residency with respect to our overall corporate structure and administrative operations, including the need to generally hold meetings of our board of directors and make decisions in Ireland, which may make certain corporate actions more cumbersome, costly and time-consuming;
- difficulties in staffing and managing foreign operations;
- foreign government taxes, regulations and permit requirements;
- U.S. and foreign government tariffs, trade restrictions, price and exchange controls and other regulatory requirements;
- anti-corruption laws, including the Foreign Corrupt Practices Act, or the FCPA;
- economic weakness, including inflation, natural disasters, war, events of terrorism or political instability in particular foreign countries;
- fluctuations in currency exchange rates, which could result in increased operating expenses and reduced revenues, and other obligations related to doing business in another country;
- compliance with tax, employment, immigration and labor laws, regulations and restrictions for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad;
- changes in diplomatic and trade relationships; and
- challenges in enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States.

Our business activities outside of the United States are subject to the FCPA and similar anti-bribery or anti-corruption laws, regulations or rules of other countries in which we operate. The FCPA and similar anti-corruption laws generally prohibit offering, promising, giving, or authorizing others to give anything of value, either directly or indirectly, to non-U.S. government officials in order to improperly influence any act or decision, secure any other 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. As described above, our business is heavily regulated and therefore involves significant interaction with public officials, including officials of non-U.S. governments. Additionally, in many other countries, the health care providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, any dealings with these prescribers and purchasers may be subject to regulation under the FCPA. Recently the SEC and the U.S. Department of Justice, or 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 are engaged in ongoing efforts that are 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 manufacturers 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, which could have a material adverse impact on our business and financial condition.

We are subject to tax audits around the world, and such jurisdictions may assess additional income tax against us. Although we believe our tax positions are reasonable, the final determination of tax audits could be materially different from our recorded income tax provisions and accruals. The ultimate results of an audit could have a material adverse effect on our operating results or cash flows in the period or periods for which that determination is made and could result in increases to our overall tax expense in subsequent periods.

These and other risks associated with our international operations may materially adversely affect our business, financial condition and results of operations.

If we fail to develop or acquire other medicine candidates or medicines, our business and prospects would be limited.

A key element of our strategy is to develop or acquire and commercialize a portfolio of other medicines or medicine candidates in addition to our current medicines, through business or medicine acquisitions. Because we do not engage in proprietary drug discovery, the success of this strategy depends in large part upon the combination of our regulatory, development and commercial capabilities and expertise and our ability to identify, select and acquire approved or clinically enabled medicine candidates for therapeutic indications that complement or augment our current medicines, or that otherwise fit into our development or strategic plans on terms that are acceptable to us. Identifying, selecting and acquiring promising medicines or medicine candidates requires substantial technical, financial and human resources expertise. Efforts to do so may not result in the actual acquisition or license of a particular medicine or medicine candidate, potentially resulting in a diversion of our management’s time and the expenditure of our resources with no resulting benefit. If we are unable to identify, select and acquire suitable medicines or medicine candidates from third parties or acquire businesses at valuations and on other terms acceptable to us, or if we are unable to raise capital required to acquire businesses or new medicines, our business and prospects will be limited.

Moreover, any medicine candidate we acquire may require additional, time-consuming development or regulatory efforts prior to commercial sale or prior to expansion into other indications, including pre-clinical studies if applicable, and extensive clinical testing and approval by the FDA and applicable foreign regulatory authorities. All medicine candidates are prone to the risk of failure that is inherent in pharmaceutical medicine development, including the possibility that the medicine candidate will not be shown to be sufficiently safe and/or effective for approval by regulatory authorities. In addition, we cannot assure that any such medicines that are approved will be manufactured or produced economically, successfully commercialized or widely accepted in the marketplace or be more effective or desired than other commercially available alternatives.

In addition, if we fail to successfully commercialize and further develop our medicines, there is a greater likelihood that we will fail to successfully develop a pipeline of other medicine candidates to follow our existing medicines or be able to acquire other medicines to expand our existing portfolio, and our business and prospects would be harmed.

We have experienced growth and expanded the size of our organization substantially in connection with our acquisition transactions, and we may experience difficulties in managing this growth as well as potential additional growth in connection with future medicine, development program or company acquisitions.

As of December 31, 2013, we employed approximately 300 full-time employees as a consolidated entity. As of December 31, 2021, we employed approximately 1,890 full-time employees, including approximately 480 sales representatives, representing a substantial change to the size of our organization. We have also experienced, and may continue to experience, turnover of the sales representatives that we hired or will hire in connection with the commercialization of our medicines, requiring us to hire and train new sales representatives. Our management, personnel, systems and facilities currently in place may not be adequate to support anticipated growth, and we may not be able to retain or recruit qualified personnel in the future due to competition for personnel among pharmaceutical businesses.

As our commercialization plans and strategies continue to develop, and particularly as we execute on our strategy to establish commercial capabilities outside the United States, we will need to continue to recruit and train sales and marketing personnel. In addition, as we build our R&D and manufacturing capabilities, we will need to continue to recruit and train qualified individuals in these areas. Our ability to manage any future growth effectively may require us to, among other things:

- continue to manage and expand the sales and marketing efforts for our existing medicines;
- enhance our operational, financial and management controls, reporting systems and procedures;
- expand our international resources;
- successfully identify, recruit, hire, train, maintain, motivate and integrate additional employees;
- establish and increase our access to commercial supplies of our medicines and medicine candidates;
- expand our facilities and equipment; and
- manage our internal development efforts effectively while complying with our contractual obligations to licensors, licensees, contractors, collaborators, distributors and other third parties.

Our acquisitions have resulted in many changes, including significant changes in the corporate business and legal entity structure, the integration of other companies and their personnel with us, and changes in systems. We may encounter unexpected difficulties or incur unexpected costs, including:

- difficulties in achieving growth prospects from combining third-party businesses with our business;
- difficulties in the integration of operations and systems;
- difficulties in the assimilation of employees and corporate cultures;
- challenges in preparing financial statements and reporting timely results at both a statutory level for multiple entities and jurisdictions and at a consolidated level for public reporting;
- challenges in keeping existing physician prescribers and patients and increasing adoption of acquired medicines;
- difficulties in achieving anticipated cost savings, synergies, business opportunities and growth prospects from the combination;
- potential unknown liabilities, adverse consequences and unforeseen increased expenses associated with the transaction; and
- challenges in attracting and retaining key personnel.

If any of these factors impair our ability to continue to integrate our operations with those of any companies or businesses we acquire, we may not be able to realize the business opportunities, growth prospects and anticipated tax synergies from combining the businesses. In addition, we may be required to spend additional time or money on integration that otherwise would be spent on the development and expansion of our business.

We may not be successful in growing our commercial operations outside the United States, and could encounter other challenges in growing our commercial presence, including due to risks associated with political and economic instability, operating under different legal requirements and tax complexities. If we are unable to manage our commercial growth outside of the United States, our opportunities to expand sales in other countries will be limited or we may experience greater costs with respect to our ex-U.S. commercial operations.

We have also broadened our acquisition strategy to include development-stage assets or programs, which entails additional risk to us. For example, if we are unable to identify programs that ultimately result in approved medicines, we may spend material amounts of our capital and other resources evaluating, acquiring and developing medicines that ultimately do not provide a return on our investment. We have less experience evaluating development-stage assets and may be at a disadvantage compared to other entities pursuing similar opportunities. Regardless, development-stage programs generally have a high rate of failure and we cannot guarantee that any such programs will ultimately be successful. While we have significantly enhanced our R&D function in recent years, we may need to enhance our clinical development and regulatory functions to properly evaluate and develop earlier-stage opportunities, which may include recruiting personnel that are knowledgeable in therapeutic areas we have not yet pursued. If we are unable to acquire promising development-stage assets or eventually obtain marketing approval for them, we may not be able to create a meaningful pipeline of new medicines and eventually realize a return on our investments. For example, a core strategic rationale for the Viela acquisition was Viela's pipeline of medicine candidates and R&D capabilities, but if we experience clinical failures with respect to Viela's medicine candidates and research programs or such candidates and programs do not otherwise result in marketed medicines, we will not realize the expected benefits from our substantial investment in the acquisition and subsequent development of the Viela pipeline. As our R&D plans and strategies continue to develop, including as a result of our acquisition of Viela, we will need to continue to recruit and train R&D personnel.

Our management may also have to divert a disproportionate amount of its attention away from day-to-day activities and toward managing these growth and integration activities. Our future financial performance and our ability to execute on our business plan will depend, in part, on our ability to effectively manage any future growth and our failure to effectively manage growth could have a material adverse effect on our business, results of operations, financial condition and prospects.

Our prior medicine and company acquisitions and any other strategic transactions that we may pursue in the future could have a variety of negative consequences, and we may not realize the benefits of such transactions or attempts to engage in such transactions.

We have completed multiple medicine and company acquisitions, and our strategy is to engage in additional strategic transactions with third parties, such as acquisitions of companies or divisions of companies and asset purchases of medicines, medicine candidates or technologies that we believe will complement or augment our existing business. We may also consider a variety of other business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and other investments. Any such transaction may require us to incur non-recurring and other charges, increase our near and long-term expenditures, pose significant integration challenges, create additional tax, legal, accounting and operational complexities in our business, require additional expertise, result in dilution to our existing shareholders and disrupt our management and business, which could harm our operations and financial results.

We face significant competition in seeking appropriate strategic transaction opportunities and the negotiation process for any strategic transaction can be time-consuming and complex. In addition, we may not be successful in our efforts to engage in certain strategic transactions because our financial resources may be insufficient and/or third parties may not view our commercial and development capabilities as being adequate. Further, increasing regulatory scrutiny of acquisitions may limit our ability to pursue certain acquisitions where we have potentially competing products or clinical programs. We may not be able to expand our business or realize our strategic goals if we do not have sufficient funding or cannot borrow or raise additional capital. There is no assurance that following any of our recent acquisition transactions or any other strategic transaction, we will achieve the anticipated revenues, net income or other benefits that we believe justify such transactions. In addition, any failures or delays in entering into strategic transactions anticipated by analysts or the investment community could seriously harm our consolidated business, financial condition, results of operations or cash flow.

We may not be able to successfully maintain our current advantageous tax status and resulting tax rates, which could adversely affect our business and financial condition, results of operations and growth prospects.

Our parent company is incorporated in Ireland and has subsidiaries maintained in Ireland and in multiple other jurisdictions. We are able to achieve a favorable tax rate through the performance of certain functions and ownership of certain assets in tax-efficient jurisdictions, including Ireland and Bermuda, together with the use of intercompany service and transfer pricing agreements, each on an arm's length basis. Our effective tax rate may be different than experienced in the past due to numerous factors including, changes to the tax laws of jurisdictions that we operate in, the enactment of new tax treaties or changes to existing tax treaties, changes in the mix of our profitability from jurisdiction to jurisdiction, the implementation of the EU Anti-Tax Avoidance Directive (see further discussion below), the implementation of the Bermuda Economic Substance Act 2018 (effective December 31, 2018) and our inability to secure or sustain acceptable agreements with tax authorities (if applicable). Any of these factors could cause us to experience an effective tax rate significantly different from previous periods or our current expectations. Taxing authorities, such as the U.S. Internal Revenue Service, or IRS, actively audit and otherwise challenge these types of arrangements, and have done so in the pharmaceutical industry. We expect that these challenges will continue as a result of the recent increase in scrutiny and political attention on corporate tax structures. The IRS and/or the Irish tax authorities may challenge our structure and transfer pricing arrangements through an audit or lawsuit. Responding to or defending such a challenge could be expensive and consume time and other resources, and divert management's time and focus from operating our business. We cannot predict whether taxing authorities will conduct an audit or file a lawsuit challenging this structure, the cost involved in responding to any such audit or lawsuit, or the outcome. If we are unsuccessful in defending such a challenge, we may be required to pay taxes for prior periods, as well as 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 medicines or seek to raise additional funds, all of which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

The IRS may not agree with our conclusion that our parent company should be treated as a foreign corporation for U.S. federal income tax purposes following the combination of the businesses of Horizon Pharma, Inc., or HPI, our predecessor, and Vidara Therapeutics International Public Limited Company, or Vidara.

Although our parent company is incorporated in Ireland, the IRS may assert that it should be treated as a U.S. corporation (and, therefore, a U.S. tax resident) for U.S. federal income tax purposes pursuant to Section 7874 of the Internal Revenue Code of 1986, as amended, or the Code. A corporation is generally considered a tax resident in the jurisdiction of its organization or incorporation for U.S. federal income tax purposes. Because our parent company is an Irish incorporated entity, it would generally be classified as a foreign corporation (and, therefore, a non-U.S. tax resident) under these general rules. Section 7874 of the Code provides an exception pursuant to which a foreign incorporated entity may, in certain circumstances, be treated as a U.S. corporation for U.S. federal income tax purposes.

We do not believe that our classification as a foreign corporation for U.S. federal income tax purposes is affected by Section 7874, though the IRS may disagree.

Recent and future changes to U.S. and non-U.S. tax laws could materially adversely affect our company.

Under current law, we expect our parent company to be treated as a foreign corporation for U.S. federal income tax purposes. However, changes to the rules in Section 7874 of the Code or regulations promulgated thereunder or other guidance issued by the U.S. Department of the Treasury, or the U.S. Treasury, or the IRS could adversely affect our parent company's status as a foreign corporation for U.S. federal income tax purposes or the taxation of transactions between members of our group, and any such changes could have prospective or retroactive application. If our parent company is treated as a domestic corporation, more of our income will be taxed by the United States which may substantially increase our effective tax rate.

In addition, the Organization for Economic Cooperation and Development, or the OECD, released its Base Erosion and Profit Shifting project final report on October 5, 2015. This report provides the basis for international standards for corporate taxation that are designed to prevent, among other things, the artificial shifting of income to tax havens and low-tax jurisdictions, the erosion of the tax base through interest deductions on intercompany debt and the artificial avoidance of permanent establishments (i.e., tax nexus with a jurisdiction). Legislation to adopt these standards has been enacted or is currently under consideration in a number of jurisdictions. On June 7, 2017, several countries, including many countries that we operate and have subsidiaries in, participated in the signing ceremony adopting the OECD's Multilateral Convention to Implement Tax Treaty Related Measures to Prevent Base Erosion and Profit Shifting, commonly referred to as the MLI. The MLI came into effect on July 1, 2018. In January 2019, Ireland deposited the instrument of ratification of Ireland's MLI choices with the OECD. Ireland's MLI came into force on May 1, 2019, however the provisions in respect of withholding taxes and other taxes levied by Ireland did not come into effect for us until January 1, 2020 (with application also depending on whether the MLI has been ratified in other jurisdictions whose tax treaties with Ireland are affected). The MLI may modify affected tax treaties making it more difficult for us to obtain advantageous tax-treaty benefits. The number of affected tax treaties could eventually be in the thousands. As a result, our income may be taxed in jurisdictions where it is not currently taxed and at higher rates of tax than it is currently taxed, which may increase our effective tax rate.

On July 12, 2016, the Anti-Tax Avoidance Directive, or ATAD, was formally adopted by the Economic and Financial Affairs Council of the EU. The stated objective of the ATAD is to provide for the effective and swift coordinated implementation of anti-base erosion and profit shifting measures at EU level. Like all directives, the ATAD is binding as to the results it aims to achieve though EU Member States are free to choose the form and method of achieving those results. In addition, the ATAD contains a number of optional provisions that present an element of choice as to how it will be implemented into law. On December 25, 2018, the Finance Act 2018 was signed into Irish law, which introduced certain elements of the ATAD, such as the Controlled Foreign Company, or CFC, regime, into Irish law. The CFC regime became effective as of January 1, 2019. The ATAD also set out a high-level framework for the introduction of Anti-hybrid provisions. Finance Act 2019 introduced Anti-hybrid legislation in Ireland with effect from January 1, 2020. Finance Act 2021 introduced further ATAD measures, such as the interest limitation rules and anti-hybrid rules to neutralize reverse-hybrid mismatches into Irish law with effect from January 1, 2022. We do not expect a material impact on our effective tax rate as a result of the introduction of these provisions.

On December 22, 2017, U.S. federal income tax legislation was signed into law (H.R. 1, "An Act to provide for reconciliation pursuant to titles II and V of the concurrent resolution on the budget for fiscal year 2018", informally titled the Tax Cuts and Jobs Act, or the Tax Act) that significantly revised the Code in the United States. The Tax Act, among other things, contained significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), implementation of a "base erosion anti-abuse tax" which requires U.S. corporations to make an alternative determination of taxable income without regard to tax deductions for certain payments to affiliates, and taxation of certain non-U.S. corporations' earnings considered to be "global intangible low taxed income", or GILTI. For example, U.S. federal income tax law resulting in additional taxes owed by U.S. shareholders under the GILTI rules, together with the Tax Act's change to the attribution rules related to "controlled foreign corporations" may discourage U.S. investors from owning or acquiring 10% or greater of our outstanding ordinary shares, which other shareholders may have viewed as beneficial or may otherwise negatively impact the trading price of our ordinary shares.

On March 27, 2020, H.R. 748, the Coronavirus Aid, Relief, and Economic Security Act was enacted in the United States, which provides temporary relief from certain aspects of the Tax Act that had imposed limitations on the utilization of certain losses, interest expense deductions, and the timing of refunds of alternative minimum tax credits.

On October 8, 2021, 136 of the 140 members of the OECD/G20 Inclusive Framework on Base Erosion and Profit Shifting, or Inclusive Framework, approved a statement providing a framework for reform of the international tax rules, or Inclusive Framework Statement. The Inclusive Framework Statement sets out the key terms for an agreement on a two-pillar solution to address the tax challenges arising from the digitalization of the economy. Pillar One focuses on nexus and profit allocation and Pillar Two provides for a global minimum effective corporate tax rate of 15 percent. The Inclusive Framework Statement provides that Pillar One would apply to multinational enterprises with annual global revenue above 20 billion euros and profitability above 10 percent, with the revenue threshold potentially reduced to 10 billion euros in the future. Based on these thresholds, we would currently be outside the scope of the Pillar One proposals. On December 20, 2021, the Inclusive Framework published detailed rules which define the scope and set out the mechanism for introducing the Pillar Two global minimum effective tax rate proposal. Although it is difficult at this stage to determine with precision the impact the Pillar Two proposals would have, their implementation could materially increase our effective tax rate.

The Biden administration and Congress have proposed various changes to the U.S. federal tax regime. Certain of these proposals include, among other things, eliminating or modifying some of the provisions enacted in the Tax Act, a new alternative minimum tax on book income and changes in the taxation of non-U.S. income. While these proposals have not yet been enacted and it is unclear whether these proposals or similar changes will ultimately ever be enacted, the passage of any legislation as a result of these proposals or similar changes in U.S. tax laws could have a material adverse impact on the value of our deferred tax assets, could result in significant one-time charges, and could increase our future U.S. tax expense.

We are unable to predict what tax laws may be proposed or enacted in the future or what effect such changes would have on our business. To the extent new tax laws are enacted, or new guidance released, this could have an adverse effect on our future effective tax rate. It could also lead to an increase in the complexity and cost of tax compliance. We urge our shareholders to consult with their legal and tax advisors with respect to the potential tax consequences of investing in or holding our ordinary shares.

If a United States person is treated as owning at least 10% of our ordinary shares, such holder may be subject to adverse U.S. federal income tax consequences.

If a United States person is treated as owning (directly, indirectly, or constructively) at least 10% of the value or voting power of our ordinary shares, such person may be treated as a “United States shareholder” with respect to each “controlled foreign corporation” in our group (if any). Because our group includes one or more U.S. subsidiaries, certain of our non-U.S. subsidiaries could be treated as controlled foreign corporations (regardless of whether or not we are treated as a controlled foreign corporation). A United States shareholder of a controlled foreign corporation may be required to report annually and include in its U.S. taxable income its pro rata share of “Subpart F income,” “global intangible low-taxed income,” and investments in U.S. property by controlled foreign corporations, regardless of whether we make any distributions. An individual that is a United States shareholder with respect to a controlled foreign corporation generally would not be allowed certain tax deductions or foreign tax credits that would be allowed to a U.S. corporation that is a United States shareholder with respect to a controlled foreign corporation. Failure to comply with these reporting and tax paying obligations may subject a United States shareholder to significant monetary penalties and may prevent the statute of limitations from starting with respect to such shareholder’s U.S. federal income tax return for the year for which reporting was due. We cannot provide any assurances that we will assist investors in determining whether any of our non-U.S. subsidiaries is treated as a controlled foreign corporation or whether any investor is treated as a United States shareholder with respect to any such controlled foreign corporation or furnish to any United States shareholders information that may be necessary to comply with the aforementioned reporting and tax paying obligations. A United States investor should consult its advisors regarding the potential application of these rules to an investment in our ordinary shares.

If we are not successful in attracting and retaining highly qualified personnel, we may not be able to successfully implement our business strategy.

Our ability to compete in the highly competitive biotechnology and pharmaceuticals industries depends upon our ability to attract and retain highly qualified managerial, manufacturing, scientific and medical personnel. We are highly dependent on our management, sales and marketing and scientific and medical personnel, including our executive officers. In order to retain valuable employees at our company, in addition to salary and annual cash incentives, we provide a mix of performance stock units, or PSUs, that vest subject to attainment of specified corporate performance goals and continued services, stock options and restricted stock units, or RSUs, that vest over time subject to continued services. The value to employees of PSUs, stock options and RSUs will be significantly affected by movements in our share price that are beyond our control, and may at any time be insufficient to counteract more lucrative offers from other companies.

Despite our efforts to retain valuable employees, members of our management, sales and marketing, regulatory affairs, clinical development, medical affairs, development and manufacturing teams may terminate their employment with us on short notice. Although we have written employment arrangements with all of our employees, these employment arrangements generally provide for at-will employment, which means that our employees can leave our employment at any time, with or without notice. The loss of the services of any of our executive officers or other key employees and our inability to find suitable replacements could potentially harm our business, financial condition and prospects. We do not maintain “key man” insurance policies on the lives of these individuals or the lives of any of our other employees. Our success also depends on our ability to continue to attract, retain and motivate highly skilled junior, mid-level, and senior managers as well as junior, mid-level, and senior sales and marketing, manufacturing, scientific and medical personnel.

Many of the other biotechnology and pharmaceutical companies with whom we compete for qualified personnel have greater financial and other resources, different risk profiles and longer histories in the industry than we do. They also may provide more diverse opportunities and better chances for career advancement. Some of these characteristics may be more appealing to high quality candidates than that which we have to offer. If we are unable to continue to attract and retain high quality personnel, the rate and success at which we can develop and commercialize medicines and medicine candidates will be limited.

We are subject to federal, state and foreign healthcare laws and regulations and implementation or changes to such healthcare laws and regulations could adversely affect our business and results of operations.

The United States and some foreign jurisdictions are considering or have enacted a number of legislative and regulatory proposals that change the healthcare system in ways that could impact profitability. In the United States and abroad there is significant interest in implementing regulations and legislation with the stated goals of containing healthcare costs, improving quality, and/or expanding access. The pharmaceutical industry has been a focus of these efforts and has been significantly affected by major legislative initiatives, particularly in the United States.

The healthcare system is highly regulated in the United States and, as a biotech company that participates in government-regulated healthcare programs, we are subject to complex laws and regulations. Violation of these laws, or any other federal or state regulations, may subject us to significant administrative, civil and/or criminal penalties, damages, disgorgement, fines, exclusion, imprisonment, additional reporting requirements, and/or oversight from federal health care programs that could require the restructuring of our operations. Any of these could have a material adverse effect on our business and financial results. Any action against us for violation of these laws, even if we ultimately are successful in our defense, will cause us to incur significant legal expenses and divert our management’s attention away from the operation of our business.

There were efforts by the Trump administration as well as Congressional and judicial actions taken to replace or weaken certain aspects of the ACA. For example, President Trump signed several executive orders and other directives designed to eliminate, delay or otherwise modify the implementation of certain provisions of the ACA. Concurrently, Congress considered legislation that would repeal and/or replace all or part of the ACA. While Congress has not passed comprehensive repeal legislation, it has enacted laws that modify certain provisions of the ACA. For example, the Tax Act included a provision which decreased, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA to \$0. Commonly referred to as the “individual mandate,” this provision imposed a fine on certain individuals who fail to maintain qualifying health coverage for all or part of the year. In addition, Congress increased the manufacturer coverage gap discount that is owed by pharmaceutical manufacturers of branded drugs and biosimilars who participate in Medicare Part D from 50% to 70%, effective January 1, 2019.

Challenges to the ACA have also taken place in courts, including the U.S. Supreme Court. For example, on June 17, 2021 the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the ACA is unconstitutional in its entirety because the “individual mandate” was repealed by Congress. Thus, the ACA will remain in effect in its current form. Further, prior to the U.S. Supreme Court ruling on January 28, 2021, President Biden issued an executive order that initiated a special enrollment period for purposes of obtaining health insurance coverage through the ACA marketplace, which began on February 15, 2021 and remained open through August 15, 2021. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is possible that the ACA will be subject to judicial or Congressional challenges in the future. It is unclear how any such challenges and the healthcare reform measures of the Biden administration will impact the ACA’s many different provisions affecting the health system, the pharmaceutical sector and our business.

In addition, drug pricing by pharmaceutical companies in the United States has come under increased scrutiny. Specifically, there have been several recent state and U.S. congressional inquiries into pricing practices by pharmaceutical companies.

In 2020, the Trump Administration advanced its agenda on drug pricing through a series of executive orders. For example, on July 24, 2020, President Trump announced several executive orders related to prescription drug pricing that attempt to implement several of the Trump Administration proposals, including a policy that would tie both Medicare Part B and Part D drug prices to international drug prices, or the “most favored nation price,” the details of which were released on September 13, 2020; one that directed HHS to finalize the Canadian drug importation proposed rule previously issued by HHS and makes other changes allowing for personal importation of drugs from Canada; one that directed HHS to finalize the rulemaking process on modifying the anti-kickback law safe harbors for plans, pharmacies, and PBMs, commonly known as the “rebate rule”; and one that reduced the cost of insulin and injectable epinephrine to patients acquired through the 340B program. Further, on August 6, 2020, the Trump administration issued another executive order that instructed the federal government to develop a list of “essential” medicines and then buy them and other medical supplies from U.S. manufacturers instead of from companies around the world. The order was meant to reduce regulatory barriers to domestic pharmaceutical manufacturing and catalyze manufacturing technologies needed to keep drug prices low and the production of drug products in the United States. The FDA issued the list of “essential” medicines pursuant to this order on October 30, 2020.

In November 2020, CMS issued an interim final rule, or IFR, implementing the Most Favored Nation, or MFN, Model basing Medicare Part B reimbursement rates for the top fifty drugs covered by Part B based to the lowest price drug manufacturers receive in OECD countries with a similar gross domestic product per capita. The MFN Model mandates participation for providers prescribing drugs included on the list and will apply in all U.S. states and territories for a seven-year period that was scheduled to begin on January 1, 2021 and end December 31, 2027. As a result of litigation challenging the Most Favored Nation model, the IFR was formally rescinded on December 27, 2021. The FDA released a final rule implementing a portion of the importation executive order providing guidance for states to build and submit importation plans. Several states have acted to implement importation plans or have introduced legislation to do so. FDA also finalized guidance for manufacturers to obtain an additional National Drug Code for an FDA-approved drug as part of a process to provide a manufacturer a means to import its drugs that were originally intended to be marketed in and authorized for sale in a foreign country. In addition, HHS and FDA are in the process of accepting industry proposals to facilitate personal importation of prescription drugs. On November 20, 2020, HHS also finalized the “rebate rule” regulation by removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through PBMs, unless the price reduction is required by law. The implementation of the rule has been delayed by the Biden Administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between PBMs, the implementation of which have also been delayed until January 1, 2023.

In July 2021, the Biden Administration released an executive order, “Promoting Competition in the American Economy,” with multiple provisions aimed at prescription drugs. In the order, the President directed the Federal Trade Commission (FTC) to ban “pay for delay” patent settlement agreements, and to identify and address any efforts that impede generic or biosimilar competition. The executive order also directed the FDA to continue to work with states and Indian Tribes to develop importation programs in accordance with Section 804 of the FDCA and FDA regulations. The order directed HHS to increase support for generic and biosimilar drugs by improving standards for the interchangeability of biologic products, supporting biosimilar adoption by increasing education, and facilitating the approval of biosimilars by updating and clarifying existing requirements and procedures related to biologics licensing. Finally, the executive order directs HHS to submit a report detailing a comprehensive plan within 45 days to fight high prescription drug prices and reduce the amount that the federal government pays for drugs. In response to President Biden’s executive order, on September 9, 2021, HHS released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform. These principles are government drug price negotiations, promoting increased competition including changes to supply chains and promoting biosimilars and generics and supporting public and private research. The plan sets out a variety of potential legislative policies that Congress could pursue as well as potential administrative actions HHS can take to advance these principles. No legislation or administrative actions have been finalized to implement the principles.

Congress continued to seek new legislative and/or administrative measures to control drug costs. Further, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug’s average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024. Finally, Congress is considering additional health reform measures, including those relating to drug pricing, as part of legislation to implement the Biden Administration’s Build Back Better initiative. This legislation includes physical infrastructure improvement and health care proposals and would use drug pricing reform as a budgetary “pay for.” This legislation is using the budget reconciliation process which requires a majority vote to pass the House and Senate. At present, the legislation has not received in the Senate. If it were to pass, it could impact the prices of drugs covered by Medicare.

In countries in the EU, legislators, policymakers, and healthcare insurance funds continue to propose and implement cost-containing measures to keep healthcare costs down, due in part to the attention being paid to healthcare cost containment in the EU. Certain of these changes could impose limitations on the prices we will be able to charge for our medicines and any approved medicine candidates or the amounts of reimbursement available for these products from governmental agencies or third-party payers, may increase the tax obligations on pharmaceutical companies such as ours, or may facilitate the introduction of generic competition with respect to our products.

The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our current medicines and/or those for which we may receive regulatory approval in the future.

We are subject, directly or indirectly, to federal and state healthcare fraud and abuse, transparency laws and false claims laws. Prosecutions under such laws have increased in recent years and we may become subject to such litigation. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

In the United States, we are subject directly, or indirectly through our customers and other third parties, to various state and federal fraud and abuse and transparency laws, including, without limitation, the federal Anti-Kickback Statute, the federal False Claims Act, the Civil Monetary Penalties Law prohibiting, among other things, beneficiary inducements, and similar state and local laws, federal and state privacy and security laws, such as the Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, sunshine laws, government price reporting laws, and other fraud laws. Some states, such as Massachusetts, make certain reported information public. In addition, there are state and local laws that require pharmaceutical representatives to be licensed and comply with codes of conduct, transparency reporting, and other obligations. Collectively, these laws may affect, among other things, our current and proposed research, sales, marketing and educational programs, as well as other possible relationships with customers, pharmacies, physicians, payers, and patients. We are subject to similar laws in the EU/EEA, including the EU General Data Protection Regulation (2016/679), or GDPR, under which fines of up to €20.0 million or up to 4% of the annual global revenue of the infringer, whichever is greater, could be imposed for significant non-compliance.

Compliance with these laws, including the development of a comprehensive compliance program, is difficult, costly and time consuming. Because of the breadth of these laws and the narrowness of available statutory and regulatory exemptions, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Moreover, state governmental agencies may propose or enact laws and regulations that extend or contradict federal requirements. These risks may be increased where there are evolving interpretations of applicable regulatory requirements, such as those applicable to manufacturer co-pay programs. Pharmaceutical manufacturer co-pay programs, including pharmaceutical manufacturer donations to patient assistance programs offered by charitable foundations, are the subject of ongoing litigation, enforcement actions and settlements (involving other manufacturers and to which we are not a party) and evolving interpretations of applicable regulatory requirements and certain state laws, and any change in the regulatory or enforcement environment regarding such programs could impact our ability to offer such programs. Other recent legislation and regulatory policies contain provisions that disincentivizes the use of co-pay coupons by requiring their value to be included in average sales price or best price calculations, potentially lowering reimbursement for drugs with a high use of copay coupons in Medicare Part B and Medicaid. If we are unsuccessful with our co-pay programs, we would be at a competitive disadvantage in terms of pricing versus preferred branded and generic competitors, or be subject to significant penalties. We are engaged in various business arrangements with current and potential customers, and we can give no assurance that such arrangements would not be subject to scrutiny under such laws, despite our efforts to properly structure such arrangements. Even if we structure our programs with the intent of compliance with such laws, there can be no certainty that we would not need to defend our business activities against enforcement or litigation. Further, we cannot give any assurances that prior business activities or arrangements of other companies that we acquire will not be scrutinized or subject to enforcement or litigation. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have an impact on our business, including the imposition of significant civil, criminal and administrative sanctions, damages, disgorgement, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, imprisonment, integrity oversight and reporting obligations, contractual damages, reputational harm, diminished profits and future earnings, and curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

There has also been a trend of increased federal and state regulation of payments made to physicians and other healthcare providers. The ACA, among other things, imposed reporting requirements on drug manufacturers for payments made by them to physicians (defined to include doctors, dentists, podiatrists, optometrists and licensed chiropractors), certain other healthcare providers (including, for example, physician assistants and nurse practitioners), and teaching hospitals, as well as ownership and investment interests held by physicians, and their immediate family members. Failure to submit required information may result in significant civil monetary penalties.

We are unable to predict whether we could be subject to other actions under any of these or other healthcare laws, or the impact of such actions. If we are found to be in violation of, or to have encouraged or assisted the violation by third parties of any of the laws described above or other applicable state and federal fraud and abuse laws, we may be subject to penalties, including significant administrative, civil and criminal penalties, damages, fines, withdrawal of regulatory approval, imprisonment, exclusion from government healthcare reimbursement programs, contractual damages, reputational harm, diminished profits and future earnings, injunctions and other associated remedies, or private “qui tam” actions brought by individual whistleblowers in the name of the government, and the curtailment or restructuring of our operations, all of which could have a material adverse effect on our business and results of operations. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management’s attention from the operation of our business.

Our medicines or any other medicine candidate that we develop may cause undesirable side effects or have other properties that could delay or prevent regulatory approval or commercialization, result in medicine re-labeling or withdrawal from the market or have a significant impact on customer demand.

Undesirable side effects caused by any medicine candidate that we develop could result in the denial of regulatory approval by the FDA or other regulatory authorities for any or all targeted indications, or cause us to evaluate the future of our development programs. In our Phase 3 clinical trial evaluating TEPEZZA for the treatment of active TED, the most commonly reported treatment-emergent adverse events were muscle spasms, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache and dry skin. With respect to KRYSTEXXA, the most commonly reported serious adverse reactions in the pivotal trial were gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis, exacerbation of pre-existing congestive heart failure and vomiting. With respect to RAVICTI, the most common side effects are diarrhea, nausea, decreased appetite, gas, vomiting, high blood levels of ammonia, headache, tiredness and dizziness. The most common side effects observed in pivotal trials for ACTIMMUNE were “flu-like” or constitutional symptoms such as fever, headache, chills, myalgia and fatigue. With respect to UPLIZNA, the most common adverse reactions across both the randomized and open-label treatment in our N-MOmentum trial for UPLIZNA were urinary tract infection, nasopharyngitis, infusion reaction, arthralgia and headache. The most common infections reported by treated patients in the randomized and open-label periods included urinary tract infection, nasopharyngitis, upper respiratory tract infection and influenza. In addition, two deaths were reported in the ongoing open-label period. One death occurred in a patient experiencing a myelitis attack and was considered unrelated to UPLIZNA by the investigator. The second death was due to complications from mechanical ventilator-associated pneumonia in a patient who developed new neurological symptoms and seizures, the cause of which could not be definitively established. The possibility that the death was treatment-related could not be ruled out, and as a result, under the terms of the protocol for the trial, the death was assessed as treatment-related. There can be no assurance a foreign regulatory authority will agree with the classifications of the deaths made by the investigators or that we will not be required to conduct additional clinical trials of UPLIZNA in order to establish an adequate safety database. With respect to PROCYSBI, the most common side effects include vomiting, nausea, abdominal pain, breath odor, diarrhea, skin odor, fatigue, rash and headache. The most common adverse events reported in a Phase 2 clinical trial of PENNSAID 2% were application site reactions, such as dryness, exfoliation, erythema, pruritus, pain, induration, rash and scabbing. The most commonly reported treatment-emergent adverse events in the Phase 3 clinical trials with RAYOS included flare in rheumatoid arthritis related symptoms, abdominal pain, nasopharyngitis, headache, flushing, upper respiratory tract infection, back pain and weight gain.

The FDA or other regulatory authorities may also require, or we may undertake, additional clinical trials to support the safety profile of our medicines or medicine candidates.

In addition, we or others may identify undesirable side effects caused by our medicines or any other medicine candidate that we may develop that receives marketing approval, or there could be perceptions that the medicine is associated with undesirable side effects. As a result of any such events it is possible that:

- regulatory authorities may require the addition of labeling statements, such as a “black box” warning or a contraindication;
- regulatory authorities may withdraw their approval of the medicine or place restrictions on the way it is prescribed;
- we may be required to change the way the medicine is administered, conduct additional clinical trials or change the labeling of the medicine or implement a risk evaluation and mitigation strategy; and
- we may be subject to increased exposure to product liability and/or personal injury claims.

If any of these events occurred with respect to our medicines, our ability to generate significant revenues from the sale of these medicines would be significantly harmed.

We rely on third parties to conduct our pre-clinical and clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines or if they experience regulatory compliance issues, we may not be able to obtain regulatory approval for or commercialize our medicine candidates and our business could be substantially harmed.

We have agreements with third-party contract research organizations, or CROs, to conduct our clinical programs, including those required for post-marketing commitments, and we expect to continue to rely on CROs for the completion of on-going and planned clinical trials. We may also have the need to enter into other such agreements in the future if we were to develop other medicine candidates or conduct clinical trials in additional indications for our existing medicines. We also rely heavily on these parties for the execution of our clinical studies and control only certain aspects of their activities. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol. We, our CROs and our academic research organizations are required to comply with current GCP or ICH regulations. The FDA, and regulatory authorities in other jurisdictions, enforce these GCP or ICH regulations through periodic inspections of trial sponsors, principal investigators and trial sites. If we or our CROs or collaborators fail to comply with applicable GCP or ICH regulations, the data generated in our clinical trials may be deemed unreliable and our submission of marketing applications may be delayed or the FDA, or such other regulatory authorities, may require us to perform additional clinical trials before approving our marketing applications. We cannot assure that, upon inspection, the FDA, or such other regulatory authorities, will determine that any of our clinical trials comply or complied with GCP or ICH regulations. In addition, our clinical trials must be conducted with medicine produced under cGMP regulations, and may require a large number of test subjects. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. Moreover, our business may be implicated if any of our CROs or collaborators violates federal or state fraud and abuse or false claims laws and regulations or privacy and security laws. We must also obtain certain third-party institutional review board, or IRB, and ethics committee approvals in order to conduct our clinical trials. Delays by IRBs and ethics committees in providing such approvals may delay our clinical trials.

If any of our relationships with these third-party CROs or collaborators terminate, we may not be able to enter into similar arrangements on commercially reasonable terms, or at all. If CROs or collaborators do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our medicines and medicine candidates. As a result, our results of operations and the commercial prospects for our medicines and medicine candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed.

Switching or adding additional CROs or collaborators can involve substantial cost and require extensive management time and focus. In addition, there is a natural transition period when a new CRO or collaborator commences work. As a result, delays may occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs and collaborators, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition or prospects. In particular, the ability of our CROs to conduct certain of their operations, including monitoring of clinical sites, has been limited by the COVID-19 pandemic, and to the extent that our CROs are unable to fulfil their contractual obligations as a result of the COVID-19 pandemic or government orders in response to the pandemic, we may have limited or no recourse under the terms of our contractual agreements with our CROs.

Clinical development of drugs and biologics involves a lengthy and expensive process with an uncertain outcome, and results of earlier studies and trials may not be predictive of future trial results.

Clinical testing is expensive and can take many years to complete, and its outcome is uncertain. Failure can occur at any time during the clinical trial process. The results of pre-clinical studies and early clinical trials of potential medicine candidates may not be predictive of the results of later-stage clinical trials. Medicine candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through pre-clinical studies and initial clinical testing.

In some instances, there can be significant variability in safety and efficacy results between different clinical trials of the same medicine candidate due to numerous factors, including changes in trial protocols, differences in size and type of the patient populations, differences in and adherence to the dosing regimen and other trial protocols and the rate of dropout among clinical trial participants. Various pipeline programs among our current pipeline are subject to this risk; for example, in a Phase 1b clinical trial, Viela observed that dazodalibep (HZN-4920) decreased disease activity in patients with rheumatoid arthritis. Viela subsequently initiated a Phase 2 clinical trial for dazodalibep (HZN-4920) in patients with rheumatoid arthritis, a separate Phase 2b clinical trial for dazodalibep (HZN-4920) in Sjögren's syndrome and a separate Phase 2 clinical trial for dazodalibep (HZN-4920) in kidney transplant rejection, which clinical trials we have assumed and are conducting. There is no assurance that dazodalibep (HZN-4920) will have a similar impact on disease activity in such clinical trials.

We may experience delays in clinical trials or investigator-initiated studies. We do not know whether any additional clinical trials will be initiated in the future, begin on time, need to be redesigned, enroll patients on time or be completed on schedule, if at all. Clinical trials can be delayed for a variety of reasons, including delays related to:

- obtaining regulatory approval to commence a trial;
- reaching agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- obtaining IRB or ethics committee approval at each site;
- recruiting suitable patients to participate in a trial;
- having patients complete a trial or return for post-treatment follow-up;
- clinical sites dropping out of a trial;
- adding new sites; or
- manufacturing sufficient quantities of medicine candidates for use in clinical trials.

Our clinical trials may also be affected by COVID-19. For example, our post-marketing clinical trials for TEPEZZA have been delayed due to the impact of the TEPEZZA supply disruption at Catalent. In addition, clinical site initiation and patient enrollment may be delayed due to staffing shortages or prioritization of hospital and healthcare resources toward COVID-19 or its variants. Current or potential patients in our ongoing or planned clinical trials may also choose to not enroll, not participate in follow-up clinical visits or drop out of the trial as a precaution against contracting COVID-19. Further, some patients may not be able or willing to comply with clinical trial protocols if quarantines impede patient movement or interrupt healthcare services. Some clinical sites in the United States have slowed or stopped further enrollment of new patients in clinical trials, denied access to site monitors or otherwise curtailed certain operations. Similarly, our ability to recruit and retain principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19, may be adversely impacted. The availability of supplies needed for the conduct of preclinical studies and clinical trials may be impacted by COVID-19 supply disruptions. For example, we depend on the availability of non-human primates to conduct certain preclinical studies that we are required to complete prior to submitting an IND and initiating clinical development. There is currently a global shortage of non-human primates available for drug development, due in part to an increase in demand from companies and other institutions developing vaccines and treatments for COVID-19. If the shortage continues, this could substantially increase the cost of conducting our preclinical development and could also result in delays to our development timelines. These events could delay our clinical trials, increase the cost of completing our clinical trials and negatively impact the integrity, reliability or robustness of the data from our clinical trials.

Patient enrollment, a significant factor in the timing of clinical trials, is affected by many factors including the size and nature of the patient population, the proximity of patients to clinical sites, the eligibility criteria for the trial, the design of the clinical trial, competing clinical trials and clinicians' and patients' perceptions as to the potential advantages of the medicine candidate being studied in relation to other available therapies, including any new drugs or biologics that may be approved for the indications we are investigating. In addition, if patients drop out of our trials, miss scheduled doses or follow-up visits or otherwise fail to follow trial protocols, or if our trials are otherwise disputed due to COVID-19 or actions taken to slow its spread, the integrity of data from our trials may be compromised or not accepted by the FDA or other regulatory authorities, which would represent a significant setback for the applicable program.

We could encounter delays if prescribing physicians encounter unresolved ethical issues associated with enrolling patients in clinical trials of our medicine candidates in lieu of prescribing existing treatments that have established safety and efficacy profiles. Further, a clinical trial may be suspended or terminated by us, our collaborators, the FDA or other regulatory authorities due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a medicine candidate, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. If we experience delays in the completion of, or if we terminate, any clinical trial of our medicine candidates, the commercial prospects of our medicine candidates will be harmed, and our ability to generate medicine revenues from any of these medicine candidates will be delayed or reduced. In addition, any delays in completing our clinical trials will increase our costs, slow down our medicine development and approval process and jeopardize our ability to commence medicine sales and generate revenues.

Moreover, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and receive compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA. The FDA may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the study. The FDA may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA and may ultimately lead to the denial of marketing approval of one or more of our medicine candidates.

Any of these occurrences may harm our business, financial condition, results of operations and prospects significantly. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our medicine candidates.

The sizes of the patient populations suffering from some of the diseases we are targeting are small and based on estimates that may not be accurate.

Because certain of our clinical trials are focused on indications with small patient populations, our ability to enroll eligible patients may be limited or may result in slower enrollment than we anticipate. In addition, our projections of both the number of people who have some of the diseases we are targeting, as well as the subset of people with these diseases who have the potential to benefit from treatment with our medicines and any of our future medicine candidates, are estimates. These estimates have been derived from a variety of sources, including scientific literature, surveys of clinics, physician interviews, patient foundations and market research, and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these diseases. The number of patients may turn out to be lower than expected. Additionally, the potentially addressable patient population for our medicines and any future medicine candidates may be limited or may not be amenable to treatment with our medicines and any of our medicine candidates, if and when approved. Even if we obtain significant market share for our medicines and any of our medicine candidates (if and when they are approved), small potential target populations for certain indications means we may never achieve profitability without obtaining market approval for additional indications.

Business interruptions could seriously harm our future revenue and financial condition and increase our costs and expenses.

Our operations could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics or health pandemics, such as the current COVID-19 pandemic, and other natural or man-made disasters or business interruptions. While we carry insurance for certain of these events and have implemented disaster management plans and contingencies, the occurrence of any of these business interruptions could seriously harm our business and financial condition and increase our costs and expenses. We conduct significant management operations at both our global headquarters located in Dublin, Ireland and our U.S. office located in Deerfield, Illinois. If our Dublin or Deerfield offices were affected by a natural or man-made disaster or other business interruption, our ability to manage our domestic and foreign operations could be impaired, which could materially and adversely affect our results of operations and financial condition. We currently rely, and intend to rely in the future, on third-party manufacturers and suppliers to produce our medicines and third-party logistics partners to ship our medicines. Our ability to obtain commercial supplies of our medicines could be disrupted and our results of operations and financial condition could be materially and adversely affected if the operations of these third-party suppliers or logistics partners were affected by a man-made or natural disaster or other business interruption. The ultimate impact of such events on us, our significant suppliers and our general infrastructure is unknown.

We are dependent on information technology systems, infrastructure and data, which exposes us to data security risks.

We generate and store sensitive data, including research data, intellectual property, personal data, and proprietary business information owned or controlled by ourselves or our employees, partners and other parties. We manage and maintain our applications and data utilizing a combination of our own on-site systems and third-party information technology systems, including cloud-based data centers and mobile technology infrastructure, both operated by third parties. We are dependent upon such systems, infrastructure and data to operate our business. The multitude and complexity of our computer systems and those of our third-party service providers makes them vulnerable to service interruption or destruction, disruption of data integrity, inadvertent actions or inactions that expose our data or systems, malicious intrusion, or random attacks. Likewise, data privacy or security incidents or breaches caused by employees or others may pose a risk that sensitive data, including our intellectual property, trade secrets or personal information of our employees, patients, customers or other business partners may be exposed to unauthorized persons or to the public. While to our knowledge, we have not experienced a material information security breach nor incurred any penalties or settlements regarding information security, cyber incidents are increasing in their frequency, sophistication and intensity.

Cyber incidents could include the deployment of harmful malware, ransomware, denial-of-service, supply chain attacks, actions or inactions by employees or other third parties with authorized access to our networks that lead to exploitation of vulnerabilities, social engineering and other means to exploit our systems and affect service reliability and threaten data confidentiality, integrity and availability. Changes in how our employees work and access our systems during the COVID-19 pandemic could lead to additional opportunities for bad actors to launch cyberattacks or for employees to cause inadvertent security risks or incidents. Our business partners, particularly our third-party service providers, face similar risks and any security breach of their systems could adversely affect our security and business posture. A security breach or privacy violation that leads to disclosure or modification of or prevents access to sensitive information or patient information, including personally identifiable information or protected health information, 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 litigation or other liability under laws and regulations that protect personal data or contractual provisions, any of which could disrupt our business and/or result in increased costs or loss of revenue. The effects of a security breach or privacy violation could be further amplified during the COVID-19 pandemic. Moreover, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property.

Despite significant efforts to create security barriers to the above described threats, it is impossible for us to entirely mitigate these risks. We may be unable to anticipate or prevent techniques used to obtain unauthorized access or to compromise our systems because they change frequently and are generally not detected until after an incident has occurred. In addition, a cybersecurity event could result in significant increases in costs, including costs for remediating the effects of such an event, fines imposed by regulators, lost revenues due to decrease in customer trust and network downtime, increases in insurance premiums due to cybersecurity incidents and damages to our reputation because of any such incident. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, there can be no assurance that our efforts will prevent service interruptions, or identify vulnerabilities or breaches in our systems, that could adversely affect our business and operations and/or result in the loss of critical, sensitive, or personal information, which could result in financial, legal, business or reputational harm to us. In addition, we cannot be certain that (a) our liability insurance will be sufficient in type or amount to cover us against claims related to security incidents, cyberattacks and other related breaches; (b) such coverage will cover any indemnification claims against us relating to any incident, will continue to be available to us on economically reasonable terms, or at all; or (c) any insurer will not deny coverage as to any future claim. The successful assertion of one or more claims against us that exceed available insurance coverage, or the occurrence of changes in our insurance policies, including premium increases or the imposition of large deductible or co-insurance requirements, could adversely affect our reputation, business, financial condition and results of operations.

We are subject to extensive worldwide laws and regulations related to data privacy and cybersecurity, and our failure to comply with these laws and regulations could harm our business.

We are subject to laws and regulations governing data privacy and the protection of personal information. These laws and regulations govern our processing of personal data, including the collection, access, use, processing, analysis, modification, storage, transfer, security breach notification, destruction and disposal of personal data. There are foreign and state law versions of these laws and regulations to which we are currently and/or may in the future, be subject. For example, the collection and use of personal health data in the EU is governed by the GDPR (and related legislation). The GDPR, which is wide-ranging in scope, imposes several requirements relating to the consent of the individuals to whom the personal data relates, the information disclosed to the individuals about our privacy practices, the security and confidentiality of the personal data, data breach notification and the use of third-party processors in connection with the processing of personal data. The GDPR also imposes strict rules on the transfer of personal data out of the EU to the United States or other jurisdictions not deemed to have adequate controls, provides an enforcement authority and imposes potentially large monetary penalties for noncompliance. The GDPR requirements apply not only to third-party transactions, but also to transfers of information within our company, including employee information. The GDPR and similar data privacy laws of other jurisdictions place significant responsibilities on us and create potential liability in relation to personal data that we or our third-party service providers process, including in clinical trials conducted in the United States and EU. In addition, we expect that there will continue to be new proposed laws, regulations and industry standards relating to privacy and data protection in the United States, the EU and other jurisdictions, and we cannot determine the impact such future laws, regulations and standards may have on our business.

The UK's vote in favor of exiting the EU, often referred to as Brexit, and ongoing developments in the UK have created uncertainty with regard to data protection regulation in the UK. As of January 1, 2021, and the expiry of transitional arrangements agreed to between the UK and EU, data processing in the UK is governed by a UK version of the GDPR (combining the GDPR and the Data Protection Act 2018), exposing us to two parallel regimes, each of which potentially authorizes similar fines and other potentially divergent enforcement actions for certain violations. As a result of the expiration of the period specified by the Trade and Cooperation Agreement, or TCA, the UK has become a 'third country' under the GDPR and transfers of data from the EEA to the UK now require an 'transfer mechanism,' such as the standard contractual clauses. On June 28, 2021, the EC announced a decision of "adequacy" concluding that the UK ensures an equivalent level of data protection to the GDPR, which removes the need for any additional transfer mechanism to be implemented at present. Some uncertainty remains, however, as this adequacy determination must be renewed after four years and may be modified or revoked in the interim. Furthermore, with the expiration of the TCA-specified period, there may be an increasing scope for divergence in application, interpretation and enforcement of the data protection law as between the UK and EEA. As a result, we may incur liabilities, expenses, costs, and other operational losses under GDPR and applicable EU Member States and the UK privacy laws in connection with any measures we take to comply with them. We cannot fully predict how the Data Protection Act, the UK GDPR, and other UK data protection laws or regulations may develop in the medium to longer term nor the effects of divergent laws and guidance regarding how data transfers to and from the UK will be regulated.

Recent legal developments in Europe have created further complexity and uncertainty regarding transfers of personal data from the EU and UK to the United States. On July 16, 2020, the Court of Justice of the European Union, or CJEU, invalidated the EU-US Privacy Shield Framework, or Privacy Shield, under which personal data could be transferred from the EU and UK to United States entities who had self-certified under the Privacy Shield scheme. Nine of our United States entities have self-certified under the Privacy Shield framework and we have entered into the standard contractual clauses within our group for transfers of data from the EU and UK to the United States. Based on current EEA and UK law, our transfers of personal data to the United States may not comply with European data protection law and may increase our exposure to the GDPR's heightened sanctions for violations of its cross-border data transfer restrictions, including fines of up to the greater of 4% of annual global revenue or €20.0 million and injunctions against transfers. While the CJEU upheld the validity of the standard contractual clauses (a standard form of contract approved by the EC as an adequate personal data transfer mechanism, and potential alternative to the Privacy Shield), it made clear that reliance on them alone may not necessarily be sufficient in all circumstances. Use of the standard contractual clauses must now be assessed on a case-by-case basis taking into account the legal regime applicable in the destination country, in particular applicable surveillance laws and rights of individuals and additional measures and/or contractual provisions may need to be put in place. The nature of these additional measures, however, remains uncertain. As supervisory authorities issue further guidance on personal data export mechanisms, including circumstances where the standard contractual clauses cannot be used, and/or start taking enforcement action, we could suffer additional costs, complaints and/or regulatory investigations or fines, and/or if we are otherwise unable to transfer personal data between and among countries and regions in which we operate, it could affect the manner in which we provide our services, the geographical location or segregation of our relevant systems and operations, and could adversely affect our financial results. On June 4, 2021, the EC adopted new standard contractual clauses under the GDPR for personal data transfers outside the EEA, which may require us to expend significant resources to update our contractual arrangements and to comply with such obligations.

Additionally, the California Consumer Privacy Act, or CCPA, went into effect on January 1, 2020. The CCPA has been dubbed the first "GDPR-like" law in the United States since it creates new individual privacy rights for consumers (as that word is broadly defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households. The CCPA requires covered companies to provide new disclosures to California consumers (as that word is broadly defined in the CCPA), provide such consumers new ways to opt-out of certain sales of personal information, and allow for a new private right of action for data breaches. It remains unclear how the CCPA will be interpreted, but as currently written, it will likely impact our business activities and exemplifies the vulnerability of our business to not only cyber threats but also the evolving regulatory environment related to personal data and protected health information. Further, California voters approved a new privacy law, the California Privacy Rights Act, or CPRA, in the November 3, 2020 election. Effective starting on January 1, 2023, the CPRA will significantly modify the CCPA, including by expanding consumers' rights with respect to certain sensitive personal information. The CPRA also creates a new state agency that will be vested with authority to implement and enforce the CCPA and the CPRA. New legislation proposed or enacted in various other states will continue to shape the data privacy environment nationally. Certain state laws, including new laws fashioned after the CCPA and CPRA, may be more stringent or broader in scope, or offer greater individual rights, with respect to confidential, sensitive and personal information than federal, international or other state laws, and such laws may differ from each other, which may complicate compliance efforts. As we expand our operations and trials (both preclinical or clinical), the CCPA and CPRA may increase our compliance costs and potential liability. Some observers have noted that the CCPA and CPRA could mark the beginning of a trend toward more stringent privacy legislation in the United States. Other states are beginning to pass similar laws, including Virginia (which passed the Consumer Data Protection Act, or CDPA, on March 2, 2021), Colorado (which enacted the Colorado Privacy Act, or CPA, that takes effect on July 1, 2023), and pending bills in Washington, New York, and Minnesota. Aspects of these state privacy statutes remain unclear, resulting in further legal uncertainty and potentially requiring us to modify our data practices and policies and to incur substantial additional costs and expenses in an effort to comply. Complying with the GDPR, CCPA, CPRA, CDPA, CPA, or other laws, regulations, amendments to or re-interpretations of existing laws and regulations, and contractual or other obligations relating to privacy, data protection, data transfers, data localization, or information security may require us to make changes to meet new legal requirements, incur substantial operational costs, modify our data practices and policies, and restrict our business operations.

Compliance with these and any other applicable privacy and data security laws and regulations is a rigorous and time-intensive process, and we may be required to put in place additional mechanisms ensuring compliance with the new data protection rules. Any actual or perceived failure by us to comply with any applicable federal, state or similar foreign laws and regulations relating to data privacy and security could result in damage to our reputation, as well as proceedings or litigation by governmental agencies or other third parties, including class action privacy litigation in certain jurisdictions, which would subject us to significant fines, sanctions, awards, penalties or judgments, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects. Furthermore, the laws are not consistent, and compliance in the event of a widespread data breach is costly.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our medicines.

We face an inherent risk of product liability claims as a result of the commercial sales of our medicines and the clinical testing of our medicine candidates. For example, we may be sued if any of our medicines or medicine candidates allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the medicine, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our medicines and medicine candidates. Even a successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our medicines or medicine candidates that we may develop;
- injury to our reputation;
- withdrawal of clinical trial participants;
- initiation of investigations by regulators;
- costs to defend the related litigation;
- a diversion of management's time and resources;
- substantial monetary awards to trial participants or patients;
- medicine recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- exhaustion of any available insurance and our capital resources; and
- the inability to commercialize our medicines or medicine candidates.

Our inability to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of medicines we develop. We currently carry product liability insurance covering our clinical studies and commercial medicine sales in the amount of \$125.0 million in the aggregate. Although we maintain such insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. If we determine that it is prudent to increase our product liability coverage due to the on-going commercialization of our current medicines in the United States, and/or the potential commercial launches of any of our medicines in additional markets or for additional indications, we may be unable to obtain such increased coverage on acceptable terms or at all. Our insurance policies also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts.

Our business involves the use of hazardous materials, and we and our third-party manufacturers must comply with environmental laws and regulations, which can be expensive and restrict how we do business.

Our third-party manufacturers' activities involve the controlled storage, use and disposal of hazardous materials owned by us, including the components of our medicine candidates and other hazardous compounds. We and our manufacturers are subject to federal, state and local as well as foreign laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. Although we believe that the safety procedures utilized by our third-party manufacturers for handling and disposing of these materials comply with the standards prescribed by these laws and regulations, we cannot eliminate the risk of accidental contamination or injury from these materials. In the event of an accident, state, federal or foreign authorities may curtail the use of these materials and interrupt our business operations. We currently only maintain Environmental Pollution Liability insurance coverage related to our South San Francisco facility and our Rockville, Maryland facility. If we are subject to any liability as a result of our third-party manufacturers' activities involving hazardous materials, our business and financial condition may be adversely affected. In the future we may seek to establish longer-term third-party manufacturing arrangements, pursuant to which we would seek to obtain contractual indemnification protection from such third-party manufacturers potentially limiting this liability exposure.

Risks Related to our Financial Position and Capital Requirements

We may not remain profitable in future periods.

Although we recorded operating income and net income for the last several years, we may incur operating losses in the future. Losses in prior periods resulted principally from costs incurred in our development activities for our medicines and medicine candidates, commercialization activities related to our medicines and costs associated with our acquisition transactions. Our prior losses, combined with possible future losses, have had and may continue to have an adverse effect on our shareholders' equity and working capital. Our ability to maintain profitability will depend on the revenues we generate from the sale of our medicines being sufficient to cover our operating expenses. We also expect our operating expenses to increase substantially as a result of continuing to develop our pipeline of medicine candidates, which will negatively impact our future profitability until such time, if ever, that these potential medicine candidates are approved and successfully commercialized, as well as developing our manufacturing and international sales and marketing capabilities.

We have limited sources of revenues and significant expenses. We cannot be certain that we will sustain profitability, which would depress the market price of our ordinary shares and could cause our investors to lose all or a part of their investment.

Our ability to sustain profitability depends upon our ability to generate sales of our medicines. The commercialization of our medicines has been primarily in the United States. We may never be able to successfully commercialize our medicines or develop or commercialize other medicines in the United States, which we believe represents our most significant commercial opportunity. Our ability to generate future revenues depends heavily on our success in:

- continued commercialization of our existing medicines and any other medicine candidates for which we obtain approval;
- securing additional foreign regulatory approvals for our medicines in territories where we have commercial rights; and
- developing, acquiring and commercializing a portfolio of other medicines or medicine candidates in addition to our current medicines.

Even if we do generate additional medicine sales, we may not be able to sustain profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the market price of our ordinary shares and could impair our ability to raise capital, expand our business, diversify our medicine offerings or continue our operations.

We may need to obtain additional financing to fund additional acquisitions.

Our operations have consumed substantial amounts of cash since inception. We expect to continue to spend substantial amounts to:

- commercialize our existing medicines in the United States, including the substantial expansion of our sales force in recent years;
- complete the regulatory approval process, and any future required clinical development related thereto, for our medicines and medicine candidates;
- potentially acquire other businesses or additional complementary medicines or medicines that augment our current commercial medicine portfolio, including costs associated with refinancing debt of acquired companies;
- satisfy progress and milestone payments under our existing and future license, collaboration and acquisition agreements; and
- conduct clinical trials with respect to potential additional indications, as well as conduct post-marketing requirements and commitments, with respect to our medicines and medicines we acquire.

While we believe that our existing cash and cash equivalents, along with future cash flows based on our current expectations of continued revenue growth, will be sufficient to fund our operations, we may need to raise additional funds if we choose to expand our commercialization or development efforts more rapidly than presently anticipated, if we develop or acquire additional medicines or acquire companies, or if our revenue does not meet expectations.

We cannot be certain that additional funding will be available on acceptable terms, or at all. As a result of the COVID-19 pandemic and actions taken to slow its spread, as well as actual or perceived changes in interest rates and economic inflation, the global credit and financial markets have at times experienced extreme volatility and disruptions, including diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. If the equity and credit markets deteriorate, it may make any additional debt or equity financing more difficult, more costly and more dilutive. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of one or more of our medicines or medicine candidates or one or more of our other R&D initiatives, or delay, cut back or abandon our plans to grow the business through acquisitions. We also could be required to:

- seek collaborators for one or more of our current or future medicine candidates at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available; or
- relinquish or license on unfavorable terms our rights to technologies or medicine candidates that we would otherwise seek to develop or commercialize ourselves.

In addition, if we are unable to secure financing to support future acquisitions, our ability to execute on a key aspect of our overall growth strategy would be impaired.

Any of the above events could significantly harm our business, financial condition and prospects.

We have incurred a substantial amount of debt, which could adversely affect our business, including by restricting our ability to engage in additional transactions or incur additional indebtedness, and prevent us from meeting our debt obligations.

As of December 31, 2021, we had \$2.6 billion book value, or \$2.6 billion aggregate principal amount of indebtedness, including \$2.0 billion in secured indebtedness.

This substantial level of debt could have important consequences to our business, including, but not limited to:

- reducing the benefits we expect to receive from our prior and any future acquisition transactions;
- making it more difficult for us to satisfy our obligations;
- requiring a substantial portion of our cash flows from operations to be dedicated to the payment of principal and interest on our indebtedness, therefore reducing our ability to use our cash flows to fund acquisitions, capital expenditures, R&D and future business opportunities;
- exposing us to the risk of increased interest rates to the extent of any future borrowings, including borrowings under our credit agreement, at variable rates of interest;
- making it more difficult for us to satisfy our obligations with respect to our indebtedness, including our outstanding notes, our credit agreement, and any failure to comply with the obligations of any of our debt instruments, including restrictive covenants and borrowing conditions, could result in an event of default under the agreements governing such indebtedness;
- increasing our vulnerability to, and reducing our flexibility to respond to, changes in our business or general adverse economic and industry conditions;
- limiting our ability to obtain additional financing for working capital, capital expenditures, debt service requirements, acquisitions, and general corporate or other purposes and increasing the cost of any such financing;
- limiting our flexibility in planning for, or reacting to, changes in our business and the industry in which we operate; and placing us at a competitive disadvantage as compared to our competitors, to the extent they are not as highly leveraged and who, therefore, may be able to take advantage of opportunities that our leverage may prevent us from exploiting; and
- restricting us from pursuing certain business opportunities.

Our credit agreement and the indenture governing our 5.5% Senior Notes due 2027, or 2027 Senior Notes, impose, and the terms of any future indebtedness may impose, various covenants that limit our ability and/or the ability of our restricted subsidiaries' (as designated under such agreements) to, among other things, pay dividends or distributions, repurchase equity, prepay junior debt and make certain investments, incur additional debt and issue certain preferred stock, incur liens on assets, engage in certain asset sales, consolidate with or merge or sell all or substantially all of our assets, enter into transactions with affiliates, designate subsidiaries as unrestricted subsidiaries, and allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to us.

Our ability to obtain future financing and engage in other transactions may be restricted by these covenants. In addition, any credit ratings will impact the cost and availability of future borrowings and our cost of capital. Our ratings at any time will reflect each rating organization's then opinion of our financial strength, operating performance and ability to meet our debt obligations. There can be no assurance that we will achieve a particular rating or maintain a particular rating in the future. A reduction in our credit ratings may limit our ability to borrow at acceptable interest rates. If our credit ratings were downgraded or put on watch for a potential downgrade, we may not be able to sell additional debt securities or borrow money in the amounts, at the times or interest rates or upon the more favorable terms and conditions that might otherwise be available. Any impairment of our ability to obtain future financing on favorable terms could have an adverse effect on our ability to refinance any of our then-existing debt and may severely restrict our ability to execute on our business strategy, which includes the continued acquisition of additional medicines or businesses.

As a result of the COVID-19 pandemic and actions taken to slow its spread, as well as actual or perceived changes in interest rates and economic inflation, the global credit and financial markets have experienced extreme volatility and disruptions, including diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. In addition, government efforts to stimulate economic activity in the face of the COVID-19 pandemic have caused interest rates to fluctuate and created uncertainty as to future fluctuations. If the equity and credit markets deteriorate, it may make any additional debt or equity financing more difficult, more costly or more dilutive.

We may not be able to generate sufficient cash to service all of our indebtedness and may be forced to take other actions to satisfy our obligations under our indebtedness, which may not be successful.

Our ability to make scheduled payments under or to refinance our debt obligations depends on our financial condition and operating performance, which is subject to prevailing economic, industry and competitive conditions and to certain financial, business and other factors beyond our control. For example, we expect that the COVID-19 pandemic and actions taken to slow its spread will continue to have a negative impact on net sales of our medicines, which will in turn negatively impact our cash flows. Our ability to generate cash flow to meet our payment obligations under our debt may also depend on the successful implementation of our operating and growth strategies. Any refinancing of our debt could be at higher interest rates and may require us to comply with more onerous covenants, which could further restrict our business operations. We cannot assure that we will maintain a level of cash flows from operating activities sufficient to pay the principal, premium, if any, and interest on our indebtedness.

If our cash flows and capital resources are insufficient to fund our debt service obligations, we may be forced to reduce or delay capital expenditures, sell assets or business operations, seek additional capital or restructure or refinance our indebtedness. We cannot ensure that we would be able to take any of these actions, that these actions would be successful and permit us to meet our scheduled debt service obligations or that these actions would be permitted under the terms of existing or future debt agreements, including the indenture that governs the 2027 Senior Notes and our credit agreement. In addition, any failure to make payments of interest and principal on our outstanding indebtedness on a timely basis would likely result in a reduction of our credit rating, which could harm our ability to incur additional indebtedness.

If we cannot make scheduled payments on our debt, we will be in default and, as a result:

- our debt holders could declare all outstanding principal and interest to be due and payable;
- the administrative agent and/or the lenders under our credit agreement could foreclose against the assets securing the borrowings then outstanding; and
- we could be forced into bankruptcy or liquidation, which could result in you losing your investment.

We generally have broad discretion in the use of our cash and may not use it effectively.

Our management has broad discretion in the application of our cash, and investors will be relying on the judgment of our management regarding the use of our cash. Our management may not apply our cash in ways that ultimately increase the value of any investment in our securities. We expect to use our existing cash to fund commercialization activities for our medicines, to potentially fund additional medicine, medicine candidate or business acquisitions, to potentially fund additional regulatory approvals of certain of our medicines, to potentially fund development, life cycle management or manufacturing activities of our medicines and medicine candidates, to potentially fund share repurchases, and for working capital, milestone payments, capital expenditures and general corporate purposes. We may also invest our cash in short-term, investment-grade, interest-bearing securities. These investments may not yield a favorable return to our shareholders. If we do not invest or apply our cash in ways that enhance shareholder value, we may fail to achieve expected financial results, which could cause the price of our ordinary shares to decline.

Our ability to use net operating loss carryforwards and certain other tax attributes to offset U.S. income taxes may be limited.

Under Sections 382 and 383 of the Code, if a corporation undergoes an “ownership change” (generally defined as a greater than 50 percent change (by value) in its equity ownership over a three-year period), the corporation’s ability to use pre-change net operating loss carryforwards and other pre-change tax attributes to offset post-change income may be limited. Certain net operating losses generated before an August 2, 2012 ownership change and federal net operating losses and federal tax credits acquired through the Viela acquisition are subject to an annual limitation. The net operating loss carryforward and tax credit carryforward limitations are cumulative such that any use of the carryforwards below the limitations in one year will result in a corresponding increase in the limitations for the subsequent tax year.

Following certain acquisitions of a U.S. corporation by a foreign corporation, Section 7874 of the Code limits the ability of the acquired U.S. corporation and its U.S. affiliates to utilize U.S. tax attributes such as net operating losses to offset U.S. taxable income resulting from certain transactions. Based on the limited guidance available, we expect this limitation is applicable for approximately ten years following our merger transaction with Vidara with respect to certain intercompany transactions. As a result, we or our other U.S. affiliates may not be able to utilize U.S. tax attributes to offset U.S. taxable income or U.S. tax liability respectively, if any, resulting from certain intercompany taxable transactions during such period. Notwithstanding this limitation, we expect that we will be able to fully use our U.S. net operating losses and tax credits prior to their expiration. As a result of this limitation, however, it may take Horizon Therapeutics USA, Inc. (formerly known as Horizon Pharma USA, Inc. and as the successor to HPI) longer to use its net operating losses and tax credits. Moreover, contrary to these expectations, it is possible that the limitation under Section 7874 of the Code on the utilization of U.S. tax attributes could prevent us from fully utilizing our U.S. tax attributes prior to their expiration if we do not generate sufficient taxable income or tax obligations.

Any limitation on our ability to use our net operating loss and tax credit carryforwards, including the carryforwards of companies that we acquire, will likely increase the taxes we would otherwise pay in future years if we were not subject to such limitations.

Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and share price.

From time to time, including recently as a result of the COVID-19 pandemic and actions taken to slow its spread, global credit and financial markets have experienced extreme volatility and disruptions, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates, and uncertainty about economic stability. Our general business strategy may be adversely affected by any such economic downturn, volatile business environment and continued unpredictable and unstable market conditions. If the equity and credit markets deteriorate, it may make any necessary debt or equity financing more difficult to complete, more costly, and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and share price and could require us to delay or abandon commercialization or development plans. There is a risk that one or more of our current service providers, manufacturers and other partners may not survive an economic down-turn, which could directly affect our ability to attain our operating goals on schedule and on budget.

At December 31, 2021, we had \$1.6 billion of cash and cash equivalents consisting of cash, money market funds, time deposits and U.S. federal government securities. While we are not aware of any downgrades, material losses, or other significant deterioration in the fair value of our cash equivalents since December 31, 2021, no assurance can be given that deterioration in conditions of the global credit and financial markets would not negatively impact our current portfolio of cash equivalents or our ability to meet our financing objectives. Dislocations in the credit market may adversely impact the value and/or liquidity of marketable securities owned by us.

The UK's referendum to leave the EU and the UK's exit from the EU on January 31, 2020, or "Brexit," has caused and may continue to cause disruptions to capital and currency markets worldwide. The full impact of Brexit, however, remains uncertain. The TCA, which outlines the trading relationship between the UK and the EU was agreed in December 2020, entered into force provisionally on January 1, 2021, and has been permanently applicable since May 1, 2021.

There remains uncertainty as to the practical impacts of Brexit and, especially in the early stages of the UK and the EU operating under different legislation, our results of operations and access to capital may be negatively affected by interest rate, exchange rate and other market and economic volatility, as well as political uncertainty. Brexit may also have a detrimental effect on our customers, distributors and suppliers, which would, in turn, adversely affect our revenues and financial condition.

While the TCA provides for the tariff-free trade of medicinal products between the UK and the EU there may be additional non-tariff costs to such trade which did not exist prior to the TCA coming into force. Further, should the UK diverge from the EU from a regulatory perspective in relation to medicinal products, tariffs could be put into place in the future. Any further changes in international trade, tariff and import/export regulations as a result of Brexit or otherwise may impose unexpected duty costs or other non-tariff barriers on us.

We could therefore, both now and in the future, face additional expenses (when compared to the position prior to the TCA coming into force) to operate our business, which could harm or delay our business. These developments, or the perception that any of them could occur, may significantly reduce global trade and, in particular, trade between the impacted nations and the UK.

If the London Inter-Bank Offered Rate, or LIBOR, is discontinued, interest payments under our credit agreement may be calculated using another reference rate.

In July 2017, the Chief Executive of the United Kingdom Financial Conduct Authority, or FCA, which regulates LIBOR, announced that the FCA intends to phase out the use of LIBOR by the end of 2021. However, the cessation date has been deferred to June 30, 2023 for the most commonly used tenors in U.S. dollar LIBOR (i.e., overnight and one, three and six months). In addition, the U.S. Federal Reserve, in conjunction with the Alternative Reference Rates Committee, a steering committee composed of large U.S. financial institutions, is considering replacing U.S. dollar LIBOR with the Secured Overnight Financing Rate, or SOFR, a new index calculated by short-term repurchase agreements, backed by Treasury securities. Although there have been certain issuances utilizing SOFR, it is unknown whether this or any other alternative reference rate will attain market acceptance as a replacement for LIBOR. LIBOR is used as a benchmark rate throughout our credit agreement, and our credit agreement does not address all circumstances in which LIBOR ceases to be published. There remains uncertainty regarding the future utilization of LIBOR and the nature of any replacement rate, and any potential effects of the transition away from LIBOR on us are not known. The transition process may involve, among other things, increased volatility and illiquidity in markets for instruments that currently rely on LIBOR and may result in increased borrowing costs, the effectiveness of related transactions such as hedges, uncertainty under applicable documentation, including the credit agreement, or difficult and costly processes to amend such documentation. As a result, our ability to refinance our credit agreement or other indebtedness or to hedge our exposure to floating rate instruments may be impaired, which would adversely affect the operations of our business. We do not expect the planned discontinuation of LIBOR to have a material impact on interest payments incurred under our credit agreement.

Changes in accounting rules or policies may affect our financial position and results of operations.

Accounting principles generally accepted in the United States, or GAAP, and related implementation guidelines and interpretations can be highly complex and involve subjective judgments. Changes in these rules or their interpretation, the adoption of new guidance or the application of existing guidance to changes in our business could significantly affect our financial position and results of operations. In addition, our operation as an Irish company with multiple subsidiaries in different jurisdictions adds additional complexity to the application of GAAP and this complexity will be exacerbated further if we complete additional strategic transactions. Changes in the application of existing rules or guidance applicable to us or our wholly-owned subsidiaries could significantly affect our consolidated financial position and results of operations.

Covenants under the indenture governing our 2027 Senior Notes and our credit agreement may 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 indenture governing the 2027 Senior Notes and the credit agreement impose various covenants that limit our ability and/or our restricted subsidiaries' ability to, among other things:

- pay dividends or distributions, repurchase equity, prepay, redeem or repurchase certain debt and make certain investments;
- incur additional debt and issue certain preferred stock;
- provide guarantees in respect of obligations of other persons;
- incur liens on assets;
- engage in certain asset sales;
- merge, consolidate with or sell all or substantially all of our assets to another person;
- enter into transactions with affiliates;
- sell assets and capital stock of our subsidiaries;
- enter into agreements that restrict distributions from our subsidiaries;
- designate subsidiaries as unrestricted subsidiaries; and
- allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to us.

These covenants may:

- limit our ability to borrow additional funds for working capital, capital expenditures, acquisitions or other general business purposes;
- limit our ability to use our cash flow or obtain additional financing for future working capital, capital expenditures, acquisitions or other general business purposes;
- 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;
- place us at a competitive disadvantage compared to less leveraged competitors; and
- increase our vulnerability to the impact of adverse economic and industry conditions.

If we are unable to successfully manage the limitations and decreased flexibility on our business due to our significant debt obligations, we may not be able to capitalize on strategic opportunities or grow our business to the extent we would be able to without these limitations.

Our failure to comply with any of the covenants could result in a default under the credit agreement or the indenture governing the 2027 Senior Notes, which could permit the administrative agent or the trustee, as applicable, or permit the lenders or the holders of the 2027 Senior Notes to cause the administrative agent or the trustee, as applicable, to declare all or part of any outstanding senior secured term loans or revolving loans, or the 2027 Senior Notes to be immediately due and payable or to exercise any remedies provided to the administrative agent or the trustee, including, in the case of the credit agreement proceeding against the collateral granted to secure our obligations under the credit agreement. An event of default under the credit agreement or the indenture governing the 2027 Senior Notes could also lead to an event of default under the terms of the other agreement. Any such event of default or any exercise of rights and remedies by our creditors could seriously harm our business.

If intangible assets that we have recorded in connection with our acquisition transactions become impaired, we could have to take significant charges against earnings.

In connection with the accounting for our various acquisition transactions, we have recorded significant amounts of intangible assets. Under GAAP, we must assess, at least annually and potentially more frequently, whether the value of goodwill has been impaired. Amortizing intangible assets will be assessed for impairment in the event of an impairment indicator. For example, during the year ended December 31, 2018, we recorded an impairment of \$33.6 million to fully write off the book value of developed technology related to PROCYSBI in Canada and Latin America. Such impairment and any reduction or other impairment of the value of goodwill or other intangible assets will result in a charge against earnings, which could materially adversely affect our results of operations and shareholders' equity in future periods.

Risks Related to Our Intellectual Property

If we are unable to obtain or protect intellectual property rights related to our medicines and medicine candidates, we may not be able to compete effectively in our markets.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our medicines and medicine candidates. The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. The patent applications that we own may fail to result in issued patents with claims that cover our medicines in the United States or in other foreign countries. If this were to occur, early generic competition could be expected against our current medicines and other medicine candidates in development. There is no assurance that all potentially relevant prior art relating to our patents and patent applications has been found, which prior art can invalidate a patent or prevent a patent from issuing based on a pending patent application.

Even if patents do successfully issue, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed or invalidated.

Any adverse outcome in these matters or any new generic challenges that may arise could result in one or more generic versions of our medicines being launched before the expiration of the listed patents, which could adversely affect our ability to successfully execute our business strategy to increase sales of our medicines, and would negatively impact our financial condition and results of operations, including causing a significant decrease in our revenues and cash flows.

Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property or prevent others from designing around our claims. If the patent applications we hold with respect to our medicines fail to issue or if their breadth or strength of protection is threatened, it could dissuade companies from collaborating with us to develop them and threaten our ability to commercialize our medicines. We cannot offer any assurances about which, if any, patents will issue or whether any issued patents will be found not invalid and not unenforceable or will go unthreatened by third parties. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file any patent application related to our medicines or any other medicine candidates. Furthermore, if third parties have filed such patent applications, an interference proceeding in the United States can be provoked by a third-party or instituted by us to determine which party was the first to invent any of the subject matter covered by the patent claims of our applications.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable, processes for which patents are difficult to enforce and any other elements of our drug discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. Although we expect all of our employees to assign their inventions to us, and all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques.

Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. For example, if the issuance, in a given country, of a patent to us, covering an invention, is not followed by the issuance, in other countries, of patents covering the same invention, or if any judicial interpretation of the validity, enforceability, or scope of the claims in, or the written description or enablement in, a patent issued in one country is not similar to the interpretation given to the corresponding patent issued in another country, our ability to protect our intellectual property in those countries may be limited. Changes in either patent laws or in interpretations of patent laws in the United States and other countries may materially diminish the value of our intellectual property or narrow the scope of our patent protection. If we are unable to prevent material disclosure of the non-patented intellectual property related to our technologies to third parties, and there is no guarantee that we will have any such enforceable trade secret protection, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition.

If we fail to comply with our obligations in the agreements under which we license rights to technology from third parties, we could lose license rights that are important to our business.

We are party to a number of technology licenses that are important to our business and expect to enter into additional licenses in the future. For example, we rely on a license from Bausch with respect to technology developed by Bausch in connection with the manufacturing of RAVICTI. The purchase agreement under which Hyperion Therapeutics, Inc., or Hyperion, purchased the rights to RAVICTI contains obligations to pay Bausch regulatory and sales milestone payments relating to RAVICTI, as well as royalties on the net sales of RAVICTI. On May 31, 2013, when Hyperion acquired BUPHENYL under a restated collaboration agreement with Bausch, Hyperion received a license to use some of the manufacturing technology developed by Bausch in connection with the manufacturing of BUPHENYL. The restated collaboration agreement also contains obligations to pay Bausch regulatory and sales milestone payments, as well as royalties on net sales of BUPHENYL. If we fail to make a required payment to Bausch and do not cure the failure within the required time period, Bausch may be able to terminate the license to use its manufacturing technology for RAVICTI and BUPHENYL. If we lose access to the Bausch manufacturing technology, we cannot guarantee that an acceptable alternative method of manufacture could be developed or acquired. Even if alternative technology could be developed or acquired, the loss of the Bausch technology could still result in substantial costs and potential periods where we would not be able to market and sell RAVICTI and/or BUPHENYL. We also license intellectual property necessary for commercialization of RAVICTI from an external party. This party may be entitled to terminate the license if we breach the agreement, including failure to pay required royalties on net sales of RAVICTI, or we do not meet specified diligence obligations in our development and commercialization of RAVICTI, and we do not cure the failure within the required time period. If the license is terminated, it may be difficult or impossible for us to continue to commercialize RAVICTI, which would have a material adverse effect on our business, financial condition and results of operations.

We hold an exclusive, worldwide license from Roche to patents and know-how for TEPEZZA. We also have exclusive sub-licenses for rights licensed to Roche for TEPEZZA by certain third-party licensors. Roche may have the right to terminate the license upon our breach, if not cured within a specified period of time. Roche may also terminate the license in the event of our bankruptcy or insolvency, or if we challenge the validity of Roche's patents. If the license is terminated for our breach or based on our challenging the validity of Roche's patents, then all rights and licenses granted to us by Roche would also terminate, and we may be required to assign and transfer to Roche certain filings and approvals, trademarks, and data in our possession necessary for the development and commercialization of TEPEZZA, and assign clinical trial agreements to the extent permitted. We may also be required to grant Roche an exclusive license under our patents and know-how for TEPEZZA, and to manufacture and supply TEPEZZA to Roche for a transitional period. If one or more of these licenses is terminated, it may be impossible for us to continue to commercialize TEPEZZA, which would have a material adverse effect on our business, financial condition and results of operations.

We also hold an exclusive license to patents and technology from Duke University, or Duke, and Mountain View Pharmaceuticals, Inc., or MVP, covering KRYSTEXXA. Duke and MVP may terminate the license if we commit fraud or for our willful misconduct or illegal conduct. Duke and MVP may also terminate the license upon our material breach of the agreement, if not cured within a specified period of time, or upon written notice if we have committed two or more material breaches under the agreement. Duke and MVP may also terminate the license in the event of our bankruptcy or insolvency. If the license is terminated, it may be impossible for us to continue to commercialize KRYSTEXXA, which would have a material adverse effect on our business, financial condition and results of operations.

We are subject to contractual obligations under our amended and restated license agreement with The Regents of the University of California, San Diego, or UCSD, as amended, with respect to PROCYSBI. If one or more of these licenses was terminated, we would have no further right to use or exploit the related intellectual property, which would limit our ability to develop PROCYSBI in other indications, and could impact our ability to continue commercializing PROCYSBI in its approved indications.

We also license rights to know-how and trademarks for ACTIMMUNE from Genentech Inc., or Genentech. Genentech may terminate the agreement upon our material default, if not cured within a specified period of time. Genentech may also terminate the agreement in the event of our bankruptcy or insolvency. Upon such a termination of the agreement, all intellectual property rights conveyed to us under the agreement, including the rights to the ACTIMMUNE trademark, revert to Genentech. If we fail to comply with our obligations under this agreement, we could lose the ability to market and distribute ACTIMMUNE, which would have a material adverse effect on our business, financial condition and results of operations.

Following our acquisition of Viela on March 15, 2021, we are a party to a number of intellectual property license agreements including (i) our licenses with Duke University and Dana-Farber Cancer Institute related to UPLIZNA, (ii) our license with SBI Biotech Co. Ltd related to daxdilimab (HZN-7734), (iii) our license with MedImmune, LLC, or MedImmune, related to dazodalibep (HZN-4920), (iv) our sublicense with MedImmune for its license with Lonza Sales AG, or Lonza, related to UPLIZNA and daxdilimab (HZN-7734), (v) our sublicense with MedImmune for its license with BioWa, Inc., or BioWa, related to UPLIZNA, and (vi) our sublicense with MedImmune for its license with BioWa and Lonza related to daxdilimab (HZN-7734). If we fail to comply with our obligations under these agreements, or we are subject to a bankruptcy, we may be required to make certain payments to the licensor, we may lose the exclusivity of our license, or the licensor may have the right to terminate the license, in which event we would not be able to develop or market products covered by the license.

We hold an exclusive license to Vectura Group plc's, or Vectura, proprietary technology and know-how covering the delayed release of corticosteroids relating to RAYOS. If we fail to comply with our obligations under our agreement with Vectura or our other license agreements, or if we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to market medicines covered by the license, including RAYOS.

Some intellectual property has been discovered through government-funded programs and thus may be subject to federal regulations such as "march-in" rights, certain reporting requirements and a preference for U.S.-based companies. Compliance with such regulations may limit our exclusive rights, and limit our ability to contract with non-U.S. manufacturers.

Some of our intellectual property rights, specifically, intellectual property rights related to UPLIZNA that are in-licensed from Duke University, were generated through the use of U.S. government funding and are therefore subject to certain federal regulations. As a result, the U.S. government may have certain rights to intellectual property embodied in certain of our current or future medicine candidates pursuant to the Bayh-Dole Act of 1980, or the Bayh-Dole Act. These U.S. government rights in certain inventions developed under a government-funded program include a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U.S. government has the right, under certain limited circumstances, to require us to grant exclusive, partially exclusive, or non-exclusive licenses to any of these inventions to a third party if it determines that: (i) adequate steps have not been taken to commercialize the invention; (ii) government action is necessary to meet public health or safety needs; or (iii) government action is necessary to meet requirements for public use under federal regulations (also referred to as "march-in rights"). To our knowledge, however, the U.S. government has, to date, not exercised any march-in rights on any patented technology that was generated using U.S. government funds. The U.S. government also has the right to take title to these inventions if we or the applicable grantee fail to disclose the invention to the government and fail to file an application to register the intellectual property within specified time limits. Intellectual property generated under a government funded program is also subject to certain reporting requirements, compliance with which may require us to expend substantial resources. In addition, the U.S. government requires that any products embodying the subject invention or produced through the use of the subject invention be manufactured substantially in the United States. The manufacturing preference requirement can be waived if the owner of the intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible. This preference for U.S. manufacturers may limit our ability to contract with non-U.S. product manufacturers for products covered by such intellectual property. To the extent any of our current or future intellectual property is generated through the use of U.S. government funding, the provisions of the Bayh-Dole Act may similarly apply.

The patent protection and patent prosecution for some of our medicine candidates is dependent on third parties.

While we normally seek and gain the right to fully prosecute the patents relating to our medicine candidates, there may be times when patents relating to our medicine candidates are controlled by our licensors. This is the case with current patents and patent applications licensed from MedImmune related to dazodalibep (HZN-4920), and those licensed from Duke University related to inebilizumab. If we, or any of our future licensing partners fail to appropriately file, prosecute and maintain patent protection for patents covering any of our medicine candidates, our ability to develop and commercialize those medicine candidates may be adversely affected and we may not be able to prevent competitors from making, using, and selling competing products. In addition, even where we now have the right to control patent prosecution of patents and patent applications we have licensed from third parties, we may still be adversely affected or prejudiced by actions or inactions of our licensors.

Risks Related to Ownership of Our Ordinary Shares

The market price of our ordinary shares historically has been volatile and is likely to continue to be volatile, and you could lose all or part of any investment in our ordinary shares.

The trading price of our ordinary shares has been volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. In addition to the factors discussed in this “Risk Factors” section and elsewhere in this report, these factors include:

- our failure to successfully execute our commercialization strategy with respect to our approved medicines, particularly our commercialization of our medicines in the United States;
- the impact of the COVID-19 pandemic on our business and industry as well as the global economy;
- actions or announcements by third-party or government payers with respect to coverage and reimbursement of our medicines;
- disputes or other developments relating to intellectual property and other proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our medicines and medicine candidates;
- unanticipated serious safety concerns related to the use of our medicines;
- adverse regulatory decisions;
- changes in laws or regulations applicable to our business, medicines or medicine candidates, including but not limited to clinical trial requirements for approvals or tax laws;
- inability to comply with our debt covenants and to make payments as they become due;
- inability to obtain adequate commercial supply for any approved medicine or inability to do so at acceptable prices;
- developments concerning our commercial partners, including but not limited to those with our sources of manufacturing supply;
- our decision to initiate a clinical trial, not to initiate a clinical trial or to terminate an existing clinical trial;
- adverse results or delays in clinical trials;
- our failure to successfully develop and/or acquire additional medicine candidates or obtain approvals for additional indications for our existing medicine candidates;
- introduction of new medicines or services offered by us or our competitors;
- overall performance of the equity markets, including the pharmaceutical sector, and general political and economic conditions;
- failure to meet or exceed revenue and financial projections that we may provide to the public;
- actual or anticipated variations in quarterly operating results;
- failure to meet or exceed the estimates and projections of the investment community;
- inaccurate or significant adverse media coverage;
- publication of research reports about us or our industry or positive or negative recommendations or withdrawal of research coverage by securities analysts;
- our inability to successfully enter new markets;
- the termination of a collaboration or the inability to establish additional collaborations;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us or our competitors;

- our inability to maintain an adequate rate of growth;
- ineffectiveness of our internal controls or our inability to otherwise comply with financial reporting requirements;
- adverse U.S. and foreign tax exposure;
- additions or departures of key management, commercial or regulatory personnel;
- issuances of debt or equity securities;
- significant lawsuits, including patent or shareholder litigation;
- changes in the market valuations of similar companies to us;
- sales of our ordinary shares by us or our shareholders in the future;
- trading volume of our ordinary shares;
- effects of natural or man-made catastrophic events or other business interruptions; and
- other events or factors, many of which are beyond our control.

In addition, the stock market in general, and The Nasdaq Global Select Market and the stock of biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may adversely affect the market price of our ordinary shares, regardless of our actual operating performance.

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

We have never declared or paid any cash dividends on our ordinary shares. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future, including due to limitations that are currently imposed by our credit agreement and the indenture governing the 2027 Senior Notes. Any return to shareholders will therefore be limited to the increase, if any, of our ordinary share price.

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.

Additional capital may be needed in the future to continue our planned operations. 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. New investors in such subsequent transactions could gain rights, preferences and privileges senior to those of holders of ordinary shares. We also maintain equity incentive plans, including our Amended and Restated 2020 Equity Incentive Plan, as amended, Amended and Restated 2018 Equity Incentive Plan, as amended, 2014 Non-Employee Equity Plan, as amended, and 2020 Employee Share Purchase Plan, and intend to grant additional ordinary share awards under these and future plans, which will result in additional dilution to our existing shareholders.

Irish law differs from the laws in effect in the United States and may afford less protection to holders of our securities.

It may not be possible to enforce court judgments obtained in the United States 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 liabilities 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 United States 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 or necessarily be enforceable in Ireland.

As an Irish company, we are governed by the Irish Companies Act 2014 (as amended), 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 and shareholder lawsuits. Likewise, the duties of directors and officers of an Irish company generally are 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 jurisdiction of the United States.

Provisions of our articles of association, and Irish law 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. For example, our articles of association:

- impose advance notice requirements for shareholder proposals and nominations of directors to be considered at shareholder meetings;
- stagger the terms of our board of directors into three classes; and
- require the approval of a supermajority of the voting power of the shares of our share capital entitled to vote generally at a meeting of shareholders to amend or repeal our articles of association.

In addition, several mandatory provisions of Irish law could prevent or delay an acquisition of us. For example, Irish law does not permit shareholders of an Irish public limited company to take action by written consent with less than unanimous consent. 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 ordinary shares in certain circumstances.

These provisions 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 could also discourage proxy contests and make it more difficult for you and our other shareholders to elect directors other than the candidates nominated by our board of directors, and could depress the market price of our ordinary shares.

Any attempts to take us over will be subject to Irish Takeover Rules and subject to review by the Irish Takeover Panel.

We are subject to the Irish Takeover Rules, under which our board of directors will not be permitted to take any action which might frustrate an offer for our ordinary shares once it has received an approach which may lead to an offer or has reason to believe an offer is imminent.

A transfer of our ordinary shares may be subject to Irish stamp duty.

In certain circumstances, the transfer of shares in an Irish incorporated company will be subject to Irish stamp duty, which is a legal obligation of the buyer. This duty is currently charged at the rate of 1.0 percent of the price paid or the market value of the shares acquired, if higher. Because our ordinary shares are traded on a recognized stock exchange in the United States, an exemption from this stamp duty is available to transfers by shareholders who hold ordinary shares beneficially through brokers, which in turn hold those shares through the Depository Trust Company, or DTC, to holders who also hold through DTC. However, a transfer by or to a record holder who holds ordinary shares directly in his, her or its own name could be subject to this stamp duty. We, in our absolute discretion and insofar as the Irish Companies Act 2014 (as amended) or any other applicable law permit, may, or may provide that one of our subsidiaries will pay Irish stamp duty arising on a transfer of our 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 us or any of our subsidiaries on behalf of the transferee, then in those circumstances, we will, on our behalf or on behalf of such 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) claim a first and permanent lien on the ordinary shares on which stamp duty has been paid by us or such subsidiary for the amount of stamp duty paid. Our lien shall extend to all dividends paid on those ordinary shares.

Dividends paid by us may be subject to Irish dividend withholding tax.

In certain circumstances, as an Irish tax resident company, we will be required to deduct Irish dividend withholding tax (currently at the rate of 25%) from dividends paid to our shareholders. Shareholders that are resident in the United States, EU countries (other than Ireland) or other countries with which Ireland has signed a tax treaty (whether the treaty has been ratified or not) generally should not be subject to Irish withholding tax so long as the shareholder has provided its broker, for onward transmission to our qualifying intermediary or other designated agent (in the case of shares held beneficially), or our or its transfer agent (in the case of shares held directly), with all the necessary documentation by the appropriate due date prior to payment of the dividend. However, some shareholders may be subject to withholding tax, which could adversely affect the price of our ordinary shares.

General Risk Factors

We have incurred and will continue to incur significant increased costs as a result of operating as a public company and our management will be required to devote substantial time to compliance initiatives.

As a public company, we have incurred and will continue to incur significant legal, accounting and other expenses. In particular, the Sarbanes-Oxley Act of 2000, or the Sarbanes-Oxley Act, as well as rules subsequently implemented by the SEC and the Nasdaq Stock Market, Inc., or Nasdaq, impose significant requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. These rules and regulations have substantially increased our legal and financial compliance costs and have made some activities more time-consuming and costly. These effects are exacerbated by our transition to an Irish company and the integration of numerous acquired businesses and operations into our historical business and operating structure. If these requirements divert the attention of our management and personnel from other business concerns, they could have a material adverse effect on our business, financial condition and results of operations. The increased costs will continue to decrease our net income or increase our net income, and may require us to reduce costs in other areas of our business or increase the prices of our medicines or services. For example, these rules and regulations make it more difficult and more expensive for us to obtain and maintain director and officer liability insurance. We cannot predict or estimate the amount or timing of additional costs that we may incur to respond to these requirements. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers. If we fail to comply with the continued listing requirements of Nasdaq, our ordinary shares could be delisted from The Nasdaq Global Select Market, which would adversely affect the liquidity of our ordinary shares and our ability to obtain future financing.

The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal controls for financial reporting and disclosure controls and procedures. In particular, we are required to perform annual system and process evaluation and testing of our internal controls over financial reporting to allow management to report on the effectiveness of our internal controls over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act, or Section 404. Our independent registered public accounting firm is also required to deliver a report on the effectiveness of our internal control over financial reporting. Our testing, or the testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses. Our compliance with Section 404 requires that we incur substantial expense and expend significant management efforts, particularly because of our Irish parent company structure and international operations. If we are not able to comply with the requirements of Section 404 or if we or our independent registered public accounting firm identify deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses, the market price of our ordinary shares could decline and we could be subject to sanctions or investigations by Nasdaq, the SEC or other regulatory authorities, which would require additional financial and management resources.

New laws and regulations as well as changes to existing laws and regulations affecting public companies, including the provisions of the Sarbanes-Oxley Act and rules adopted by the SEC and by Nasdaq, would likely result in increased costs as we respond to their requirements.

Securities class action litigation could divert our management's attention and harm our business and could subject us to significant liabilities.

The stock markets have from time to time experienced significant price and volume fluctuations that have affected the market prices for the equity securities of pharmaceutical companies. These broad market fluctuations may cause the market price of our ordinary shares to decline. In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology and biopharma companies have experienced significant stock price volatility in recent years. For example, following declines in our stock price, two federal securities class action lawsuits were filed in March 2016 against us and certain of our current and former officers alleging violations of the Securities Exchange Act of 1934, as amended, which lawsuits were dismissed by the plaintiffs in June 2018. Even if we are successful in defending any similar claims that may be brought in the future, such litigation could result in substantial costs and may be a distraction to our management and may lead to an unfavorable outcome that could adversely impact our financial condition and prospects.

Our employees, independent contractors, principal investigators, consultants, vendors, distributors and CROs may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk that our employees, independent contractors, principal investigators, consultants, vendors, distributors and CROs may engage in fraudulent or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or unauthorized activities that violate FDA regulations, including those laws that require the reporting of true, complete and accurate information to the FDA, manufacturing standards, federal and state healthcare fraud and abuse laws and regulations, and laws that require the true, complete and accurate reporting of financial information or data. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Misconduct by our employees and other third parties may also include the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. We have adopted a Code of Conduct and Ethics, but it is not always possible to identify and deter misconduct by our employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs and imprisonment.

Third-party claims of intellectual property infringement may prevent or delay our development and commercialization efforts.

Our commercial success depends in part on us avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions and inter party reexamination proceedings before the United States Patent and Trademark Office, or the U.S. PTO. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which our collaborators are developing medicine candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our medicine candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our medicines and/or any other medicine candidates. Because patent applications can take many years to issue, there may be currently pending patent applications, which may later result in issued patents that our medicine candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our medicine candidates, any molecules formed during the manufacturing process or any final medicine itself, the holders of any such patents may be able to block our ability to commercialize such medicine candidate unless we obtained a license under the applicable patents, or until such patents expire. Similarly, if any third-party patent were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, including combination therapy, the holders of any such patent may be able to block our ability to develop and commercialize the applicable medicine candidate unless we obtained a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our medicine candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties or redesign our infringing medicines, which may be impossible or require substantial time and monetary expenditure. We cannot predict whether any such license would be available at all or whether it would be available on commercially reasonable terms. Furthermore, even in the absence of litigation, we may need to obtain licenses from third parties to advance our research or allow commercialization of our medicine candidates, and we have done so from time to time. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In that event, we would be unable to further develop and commercialize one or more of our medicine candidates, which could harm our business significantly. We cannot provide any assurances that third-party patents do not exist which might be enforced against our medicines, resulting in either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that one of our patents, or a patent of one of our licensors, is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing.

There are numerous post grant review proceedings available at the U.S. PTO (including inter partes review, post-grant review and ex-parte reexamination) and similar proceedings in other countries of the world that could be initiated by a third-party that could potentially negatively impact our issued patents.

Interference proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our collaborators or licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our ordinary shares.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees on any issued patent are due to be paid to the U.S. PTO and foreign patent agencies in several stages over the lifetime of the patent. The U.S. PTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we or licensors that control the prosecution and maintenance of our licensed patents fail to maintain the patents and patent applications covering our medicine candidates, our competitors might be able to enter the market, which would have a material adverse effect on our business.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties.

We employ individuals who were previously employed at other biotechnology or pharmaceutical companies. We may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed confidential information of our employees' former employers or other third parties. We may also be subject to claims that former employers or other third parties have an ownership interest in our patents. Litigation may be necessary to defend against these claims. There is no guarantee of success in defending these claims, and even if we are successful, litigation could result in substantial cost and be a distraction to our management and other employees.

Sales of a substantial number of our ordinary shares in the public market could cause our share price to decline.

If our existing shareholders sell, or indicate an intention to sell, substantial amounts of our ordinary shares in the public market, the trading price of such ordinary shares could decline. In addition, our ordinary shares that are either subject to outstanding options and restricted stock units or reserved for future issuance under our employee benefit plans are or may become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules and the Securities Act of 1933, as amended. If these additional ordinary shares are sold, or if it is perceived that they will be sold, in the public market, the trading price of our ordinary shares could decline.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our share price and trading volume could decline.

The trading market for our ordinary shares will depend in part on the research and reports that securities or industry analysts publish about us or our business. If one or more of the analysts who cover us downgrade our rating or publish inaccurate or unfavorable research about our business, our share price could decline. If one or more of these analysts cease coverage of our company or fail to publish reports on our company regularly, demand for our ordinary shares could decrease, which might cause our share price and trading volume to decline.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

As of December 31, 2021, we have the following office space lease agreements in place for real properties:

Location	Approximate Square Footage	Lease Expiry Date
Dublin, Ireland (St. Stephen's Green) ⁽¹⁾	63,000	May 4, 2041
Lake Forest, Illinois	160,000	March 31, 2031
South San Francisco, California	20,000	January 31, 2030
Rockville, Maryland ⁽²⁾	24,500	August 31, 2023 to April 30, 2026
Chicago, Illinois	9,200	December 31, 2028
Gaithersburg, Maryland ⁽²⁾	7,200	June 30, 2022
Washington, D.C.	6,000	September 30, 2024
Mannheim, Germany	4,800	December 31, 2022

- (1) In October 2019, we entered into an agreement for lease relating to approximately 63,000 square feet of office space under construction on St. Stephen's Green in Dublin, Ireland. In May 2021, the construction of the office was completed by the lessor and the lease became effective. As a result, we recognized \$60.9 million as a right-of-use asset and a corresponding lease liability on the consolidated balance sheet. The lease is due to expire in May 2041. We incurred leasehold improvement costs during 2021 in order to prepare the building for occupancy. On November 1, 2021, we moved our Connaught House office employees to the St. Stephen's Green office. In July 2021, we entered into an agreement to assign the Connaught House lease to a third party and the lease assignment became effective on November 1, 2021.
- (2) On March 15, 2021, we completed our acquisition of Viela. As part of the acquisition, we assumed two leases in Rockville, Maryland for both office and laboratory space and a lease in Gaithersburg, Maryland for office space. On March 18, 2021, we entered into a third lease in Rockville, Maryland for office and laboratory space, with a lease commencement date of April 1, 2021.

The above table does not include details of an agreement to lease entered into in November 2021 relating to approximately 192,000 square feet of office and laboratory space under construction in Rockville, Maryland. Lease commencement will begin when construction of the building is completed by the lessor and we have access to begin the construction of leasehold improvements. We expect to receive access to the office and laboratory space and commence the related lease in the first half of 2023 and incur leasehold improvement costs through 2024 in order to prepare the building for occupancy.

Effective January 1, 2022, the South San Francisco, California office lease was amended to include an additional suite with approximately 20,000 square feet and the lease term on the existing lease was extended to December 31, 2031. In addition, in January 2022, we entered a sublease agreement for the entire Lake Forest office building for the remaining term of the original lease through March 31, 2031.

Item 3. Legal Proceedings

For a description of our legal proceedings, see Note 16 of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K.

Item 4. Mine Safety Disclosures

None.

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 “HZNP”.

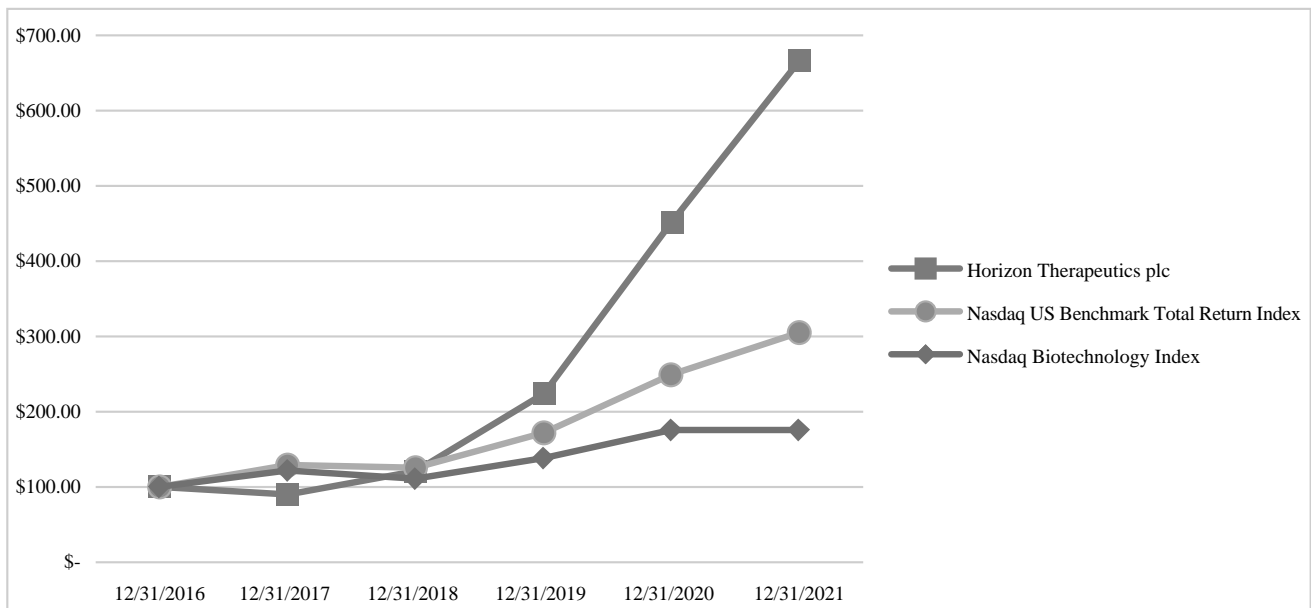
Holder of Record

The closing price of our ordinary shares on February 23, 2022 was \$91.46. As of February 23, 2022, there were approximately nine 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.

Performance Graph

The following graph shows a comparison from December 31, 2016, through December 31, 2021, of the cumulative total return for (i) our ordinary shares, (ii) the Nasdaq Biotechnology Index and (iii) the Nasdaq U.S. Benchmark Total Return Index.

Information set forth in the graph below represents the performance of our ordinary shares from December 31, 2016, through December 31, 2021. The graph assumes an initial investment of \$100.00 on December 31, 2016. The comparisons in the graph are required by the Securities and Exchange Commission and are not intended to forecast or be indicative of possible future performance of our ordinary shares.



	12/31/2016	12/31/2017	12/31/2018	12/31/2019	12/31/2020	12/31/2021
Cumulative Returns						
Horizon Therapeutics plc	\$ 100.00	\$ 90.23	\$ 120.77	\$ 223.73	\$ 452.10	\$ 666.01
Nasdaq Biotechnology Index	100.00	121.63	110.85	138.69	175.33	175.37
Nasdaq U.S. Benchmark Total Return Index	100.00	129.64	125.96	172.17	249.51	304.85

The foregoing graph and table are furnished solely with this report, and are not filed with this report, and shall not be deemed incorporated by reference into any other filing under the Securities Act of 1933, as amended, or the Securities Act, or the Securities Exchange Act of 1934, as amended, whether made by us before or after the date hereof, regardless of any general incorporation language in any such filing, except to the extent we specifically incorporate this material by reference into any such filing.

Dividend Policy

We have never declared or paid cash dividends on our common equity. We currently intend to retain all available funds and any future earnings to support operations and finance the growth and development of our business and do not intend to pay cash dividends on our ordinary shares for the foreseeable future. Under Irish law, dividends may only be paid, and share repurchases and redemptions must generally be funded only out of, “distributable reserves”. In addition, we are currently prohibited from paying cash dividends by the terms of our credit agreement with Citibank, N.A., as administrative and collateral agent and our \$600.0 million aggregate principal amount of 5.5% Senior Notes due 2027, subject to customary exceptions. 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 and other factors our board of directors deems relevant.

Securities Authorized for Issuance under Equity Compensation Plans

See Item 12 of Part III of this Annual Report on Form 10-K regarding information about securities authorized for issuance under our equity compensation plans.

Recent Sales of Unregistered Securities

Except as previously reported in our Quarterly Reports on Form 10-Q and Current Reports on Form 8-K filed with the 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.

Issuer Repurchases of Equity Securities

None.

Irish Law Matters

See *Irish Law Matters* included in Item 1 of Part I of this Annual Report on Form 10-K.

Item 6. [Reserved.]

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

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and the related notes appearing at the end of this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. You should read the “Risk Factors” section of this Annual Report on Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

This section of this Annual Report on Form 10-K generally discusses 2021 and 2020 items and year-to-year comparisons between 2021 and 2020. Discussions of 2019 items and year-to-year comparisons between 2020 and 2019 that are not included in this Annual Report on Form 10-K can be found in “Management’s Discussion and Analysis of Financial Condition and Results of Operations” in Part II, Item 7 of our Annual Report on Form 10-K for the fiscal year ended December 31, 2020, filed with the Securities and Exchange Commission on February 24, 2021.

Unless otherwise indicated or the context otherwise requires, references to “Horizon”, “we”, “us” and “our” refer to Horizon Therapeutics plc and its consolidated subsidiaries.

OUR BUSINESS

We are focused on the discovery, development and commercialization of medicines that address critical needs for people impacted by rare, autoimmune and severe inflammatory diseases. Our pipeline is purposeful: we apply scientific expertise and courage to bring clinically meaningful therapies to patients. We believe science and compassion must work together to transform lives. We have two reportable segments, the orphan segment and the inflammation segment, and our commercial portfolio is currently composed of 12 medicines in the areas of rare diseases, gout, ophthalmology and inflammation.

In July 2021, we completed the purchase of a biologic drug product manufacturing facility from EirGen Pharma Limited, or EirGen, a subsidiary of OPKO Health, Inc., in Waterford, Ireland for \$67.9 million. Refer to Note 4, *Acquisitions, Divestitures and other Arrangements*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K, for further details.

On March 15, 2021, we completed the acquisition of Viela Bio, Inc., or Viela. The acquisition expanded our commercial medicine portfolio by adding an additional rare disease medicine, UPLIZNA[®], to our orphan segment. The Viela acquisition also provides multiple opportunities to drive long-term growth and solidify our future as an innovation-driven biotech company. Viela’s mid-stage biologics pipeline, research and development, or R&D, team and on-market medicine UPLIZNA, made it a complementary strategic fit with our pipeline, commercial portfolio and therapeutic areas of focus. Refer to Note 4, *Acquisitions, Divestitures and other Arrangements*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K, for further details.

As of December 31, 2021, our commercial portfolio consisted of the following medicines:

Orphan

TEPEZZA[®] (teprotumumab-trbw), for intravenous infusion
KRYSTEXXA[®] (pegloticase injection), for intravenous infusion
RAVICTI[®] (glycerol phenylbutyrate) oral liquid
PROCYSBI[®] (cysteamine bitartrate) delayed-release capsules and granules, for oral use
ACTIMMUNE[®] (interferon gamma-1b) injection, for subcutaneous use
UPLIZNA (inebilizumab-cdon) injection, for intravenous use
BUPHENYL[®] (sodium phenylbutyrate) tablets and powder, for oral use
QUINSAIR[™] (levofloxacin) solution for inhalation

Inflammation

PENNSAID[®] (diclofenac sodium topical solution) 2% w/w, or PENNSAID 2%, for topical use
DUEXIS[®] (ibuprofen/famotidine) tablets, for oral use
RAYOS[®] (prednisone) delayed-release tablets, for oral use
VIMOVO[®] (naproxen/esomeprazole magnesium) delayed-release tablets, for oral use

Impact of COVID-19

See Item 1 of Part I, *Business*, of this Annual Report on Form 10-K regarding information about the impact of COVID-19 on our company.

Acquisitions and Divestitures

Since January 1, 2019, we completed the following acquisitions and divestitures:

- In July 2021, we completed the purchase of a biologic drug product manufacturing facility from EirGen in Waterford, Ireland for \$67.9 million.
- In March 2021, we completed the acquisition of Viela, in which we acquired all of the issued and outstanding shares of Viela's common stock for \$53.00 per share in cash. The total consideration for the acquisition was approximately \$3.0 billion, including cash acquired of \$342.3 million.
- In October 2020, we sold our rights to develop and commercialize RAVICTI and BUPHENYL in Japan to Medical Need Europe AB, part of the Immedica Group. We have retained the rights to RAVICTI and BUPHENYL in North America.
- In April 2020, we acquired Curzion Pharmaceuticals, Inc., or Curzion, a privately held development-stage biopharma company, and its development-stage oral selective lysophosphatidic acid 1 receptor (LPAR1) antagonist, CZN001 (renamed HZN-825), for an upfront cash payment of \$45.0 million with additional payments contingent on the achievement of development and regulatory milestones.
- In June 2019, we sold our rights to MIGERGOT to Cosette Pharmaceuticals, Inc., for an upfront payment and potential additional contingent consideration payments, or the MIGERGOT transaction.
- Effective January 2019, we amended our license and supply agreements with Jagotec AG and Skyepharma AG, which are affiliates of Vectura Group plc, or Vectura. Under these amendments, our rights to LODOTRA in Europe were transferred to Vectura.

The consolidated financial statements presented herein include the results of operations of the acquired businesses from the applicable dates of acquisition. Refer to Note 4, *Acquisitions, Divestitures and other Arrangements*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K, for further details of our acquisitions and divestitures.

Strategy

Horizon is a leading high-growth, innovation-driven, profitable biotech company. We are focused on the discovery, development and commercialization of medicines that address critical needs for people impacted by rare, autoimmune and severe inflammatory diseases. Our three strategic goals are to: (i) maximize the benefit and value of our on-market medicines through commercial execution and clinical investment; (ii) expand our pipeline through significant investment in R&D and business development; and (iii) build a global presence in targeted international markets. Our vision is to build healthier communities, urgently and responsibly, supported by our philosophy to make a meaningful difference for patients and communities in need. We believe this generates value for our multiple stakeholders, including our shareholders.

Our commercialization strategy for our on-market rare disease medicines, including our key growth drivers TEPEZZA and KRYSTEXXA, includes efforts to increase awareness of the conditions each medicine is designed to treat, enhancing efforts to identify target patients and promote earlier treatment; drive awareness of the benefits of the medicines; optimize timely access for patients to the medicines; and maximize the value of the medicines through investment in clinical trials. For our key growth driver UPLIZNA, which we added to our portfolio with the Viela acquisition, in addition to our overall commercial strategy, our commercialization strategy also includes investing in the commercial and clinical support infrastructure as well as increasing awareness of what differentiates UPLIZNA from other medicines by generating additional trial data analyses and clinical evidence. We are leveraging the successful strategies we have used with TEPEZZA and KRYSTEXXA to support our commercial efforts for UPLIZNA.

Our R&D strategy is to expand our pipeline of preclinical and clinical development programs to drive sustainable growth, as well as maximizing the benefit and value of our existing medicines through development programs. Towards expanding our pipeline, we are using a balanced approach of internal research and external collaborations while remaining aligned with our core focus areas. We are (i) acquiring, licensing and developing medicines for indications that address unmet needs in rare, autoimmune and severe inflammatory diseases, particularly those in our therapeutic areas of focus; (ii) leveraging our internal research as well as research-based partnerships and collaborations to drive earlier-stage innovation; (iii) maximizing the range of potential diseases our pipeline medicine candidates can impact; and (iv) continuing to build out our research capabilities to generate earlier-stage candidates internally. The March 2021 acquisition of Viela and the addition of its mid-stage biologics pipeline significantly expanded our pipeline and expanded our therapeutic areas of focus to include neuroimmunology, dermatology and respiratory, in addition to rheumatology, ophthalmology, nephrology and endocrinology. In the third quarter of 2021, we announced the addition of five additional Phase 2 development programs in new disease states for two of our pipeline candidates. In addition, we expanded our earlier-stage discovery pipeline of novel therapeutic programs in 2021 through global in-licensing agreements with Arrowhead Pharmaceuticals, Inc., or Arrowhead, and Alpine Immune Sciences, Inc., or Alpine. At the end of 2021, our R&D pipeline included more than 20 programs, with 16 of them added during the year. Also in 2021, we successfully completed two Phase 4 clinical trials designed to maximize the benefit and value of KRYSTEXXA.

The aim of our global expansion strategy is to build a global presence in targeted international markets and we made significant progress in 2021 in support of this strategy. In November 2021, we announced that the Committee for Medicinal Products for Human Use of the European Medicines Agency has adopted a positive opinion recommending grant of a Centralised Marketing Authorisation, or CMA, for UPLIZNA as a monotherapy for the treatment of adult patients with neuromyelitis optica spectrum disorder, or NMOSD, who are anti-aquaporin-4 immunoglobulin G seropositive (AQP4-IgG+). While the Committee for Orphan Medicinal Products did not recommend maintenance of the orphan designation for UPLIZNA following its review, we are continuing to invest in our European infrastructure to support a potential European launch of UPLIZNA for NMOSD, which we anticipate would begin with Germany in the second quarter of 2022, assuming the grant of a CMA by the EC. We advanced our efforts to bring TEPEZZA to patients with TED in targeted markets outside of the United States, including Japan, where we initiated a Phase 3 randomized, placebo-controlled clinical trial for the treatment of moderate-to-severe active TED patients. We acquired a biologic drug product manufacturing facility in Waterford, Ireland, in the second quarter of 2021, which will support growth of our on-market and development-stage biologics as well as our global expansion. Subject to completing the build-out, validation and regulatory approval processes, we expect the first medicine manufactured at the facility to be approved for release in 2023.

RESULTS OF OPERATIONS

Year Ended December 31, 2021 Compared to Year Ended December 31, 2020

Consolidated Results

	For the Years Ended December 31,		Change \$	Change %
	2021	2020		
	(in thousands, except percentages)			
Net sales	\$ 3,226,410	\$ 2,200,429	\$ 1,025,981	47%
Cost of goods sold	794,512	532,695	261,817	49%
Gross profit	2,431,898	1,667,734	764,164	46%
Operating expenses:				
Research and development	431,990	209,364	222,626	106%
Selling, general and administrative	1,446,410	973,227	473,183	49%
Impairment of long-lived asset	12,371	—	12,371	100%
Gain on sale of assets	(2,000)	(4,883)	2,883	(59)%
Total operating expenses	1,888,771	1,177,708	711,063	60%
Operating income	543,127	490,026	53,101	11%
Other expense, net:				
Interest expense, net	(81,063)	(59,616)	(21,447)	36%
Foreign exchange loss	(1,028)	(297)	(731)	246%
Other income, net	1,791	3,388	(1,597)	(47)%
Loss on debt extinguishment	—	(31,856)	31,856	(100)%
Total other expense, net	(80,300)	(88,381)	8,081	(9)%
Income before (benefit) expense for income taxes	462,827	401,645	61,182	15%
(Benefit) expense for income taxes	(71,664)	11,849	(83,513)	(705)%
Net income	\$ 534,491	\$ 389,796	\$ 144,695	37%

Net sales. Net sales increased \$1,026.0 million, or 47%, to \$3,226.4 million during the year ended December 31, 2021, from \$2,200.4 million during the year ended December 31, 2020. The increase in net sales during the year ended December 31, 2021 was primarily due to an increase in net sales in our orphan segment of \$1,107.9 million. Growth was primarily due to an increase in TEPEZZA net sales of \$841.3 million, an increase in KRYSTEXXA net sales of \$159.6 million and net sales generated by UPLIZNA of \$60.8 million, partially offset by a decrease in net sales in our inflammation segment of \$81.9 million when compared to the year ended December 31, 2020.

The following table presents a summary of total net sales attributed to geographic sources for the years ended December 31, 2021 and 2020 (in thousands, except percentages):

	Year Ended December 31, 2021		Year Ended December 31, 2020	
	Amount	% of Total Net Sales	Amount	% of Total Net Sales
United States	\$ 3,210,020	100%	\$ 2,191,111	100%
Rest of world	16,390	*	9,318	*
Total net sales	\$ 3,226,410		\$ 2,200,429	

*Less than 1%

The following table reflects the components of net sales for the years ended December 31, 2021 and 2020 (in thousands, except percentages):

	Year Ended December 31,		Change \$	Change %
	2021	2020		
TEPEZZA	\$ 1,661,299	\$ 820,008	\$ 841,291	103%
KRYSTEXXA	565,452	405,849	159,603	39%
RAVICTI	291,945	261,615	30,330	12%
PROCYSBI	189,965	170,102	19,863	12%
ACTIMMUNE	117,164	118,834	(1,670)	(1)%
UPLIZNA	60,805	—	60,805	100%
BUPHENYL	7,860	10,549	(2,689)	(25)%
QUINSAIR	1,028	698	330	47%
Orphan segment net sales	\$ 2,895,518	\$ 1,787,655	\$ 1,107,863	62%
PENNSAID 2%	191,621	178,011	13,610	8%
DUEXIS	74,023	125,331	(51,308)	(41)%
RAYOS	56,851	71,811	(14,960)	(21)%
VIMOVO	8,397	37,621	(29,224)	(78)%
Inflammation segment net sales	\$ 330,892	\$ 412,774	\$ (81,882)	(20)%
Total net sales	\$ 3,226,410	\$ 2,200,429	\$ 1,025,981	47%

Orphan Segment

TEPEZZA. Net sales increased \$841.3 million, or 103%, to \$1,661.3 million during the year ended December 31, 2021, from \$820.0 million during the year ended December 31, 2020. Net sales primarily increased due to volume growth of approximately \$830.3 million. In December 2020, pursuant to the Defense Production Act of 1950, Catalent Indiana, LLC, or Catalent, was ordered to prioritize certain COVID-19 vaccine manufacturing, resulting in the cancellation of previously guaranteed and contracted *TEPEZZA* drug product manufacturing slots in December 2020, which were required to maintain *TEPEZZA* supply. In March 2021, the U.S. Food and Drug Administration, or FDA, approved a prior approval supplement to the *TEPEZZA* biologics license application (which was previously approved in January 2020), giving us authorization to manufacture more *TEPEZZA* drug product in a batch resulting in an increased number of vials with each manufacturing slot. We commenced resupply of *TEPEZZA* to the market in April 2021. Refer to the *Impact of COVID-19* section in Item 1 of Part I, *Business*, of this Annual Report on Form 10-K above, for further information.

KRYSTEXXA. Net sales increased \$159.6 million, or 39%, to \$565.4 million during the year ended December 31, 2021, from \$405.8 million during the year ended December 31, 2020. Net sales increased by approximately \$106.2 million due to volume growth and \$53.4 million due to higher net pricing.

RAVICTI. Net sales increased \$30.3 million, or 12%, to \$291.9 million during the year ended December 31, 2021, from \$261.6 million during the year ended December 31, 2020. Net sales increased by approximately \$32.3 million due to volume growth, partially offset by a decrease of approximately \$2.0 million due to lower net pricing.

PROCYSBI. Net sales increased \$19.9 million, or 12%, to \$190.0 million during the year ended December 31, 2021, from \$170.1 million during the year ended December 31, 2020. Net sales increased by approximately \$12.0 million due to higher net pricing and \$7.9 million due to volume growth.

ACTIMMUNE. Net sales decreased \$1.7 million, or 1%, to \$117.1 million during the year ended December 31, 2021, from \$118.8 million during the year ended December 31, 2020. Net sales decreased by approximately \$4.4 million due to lower sales volume, partially offset by an increase of approximately \$2.7 million resulting from higher net pricing.

UPLIZNA. Net sales generated by *UPLIZNA* during the year ended December 31, 2021 were \$60.8 million. We began recognizing *UPLIZNA* sales following our acquisition of Viela on March 15, 2021.

Inflammation Segment

At September 30, 2021, we determined that there was an indicator to trigger an interim impairment analysis of the inflammation reporting unit's \$56.2 million goodwill balance. The fair value of the inflammation reporting unit exceeded its carrying value by more than 30% as of September 30, 2021, the interim testing date, resulting in no impairment. In order to evaluate the sensitivity of the fair value calculations on the goodwill impairment test, we applied a hypothetical 10 percent decrease to the fair values of the reporting unit. A 10% decrease in fair value would reduce the headroom between the reporting unit's fair value and its carrying value to approximately 19%.

In addition, our annual, qualitative goodwill impairment test performed for both the orphan and inflammation reporting unit in the fourth quarter of 2021 did not indicate an impairment. While no impairment was recognized during the year ended December 31, 2021, we anticipate that an impairment of the inflammation reporting unit's goodwill could occur in the next 12 to 18 months if the reporting unit does not achieve currently forecasted net sales and profitability estimates. These forecasts and estimates could be impacted by factors outside of our control, such as increased competition from RAYOS generic entrants, which may result in an impairment.

PENNSAID 2%. Net sales increased \$13.6 million, or 8%, to \$191.6 million during the year ended December 31, 2021, from \$178.0 million during the year ended December 31, 2020. Net sales increased by approximately \$21.8 million resulting from higher net pricing primarily due to lower utilization of our patient assistance programs, partially offset by a decrease of approximately \$8.2 million resulting from lower sales volume.

DUEXIS. Net sales decreased \$51.3 million, or 41%, to \$74.0 million during the year ended December 31, 2021, from \$125.3 million during the year ended December 31, 2020. Net sales decreased by approximately \$44.0 million resulting from lower sales volume, primarily due to the impact of generic competition on DUEXIS, and a decrease of approximately \$7.3 million due to lower net pricing.

On August 4, 2021, following a judgment in the District Court of Delaware, which was subsequently affirmed by the Federal Circuit Court of Appeals on November 16, 2021, Alkem Laboratories, Inc., or Alkem, launched a generic version of DUEXIS in the United States. As a result, we have repositioned our promotional efforts previously directed to DUEXIS to the other inflammation segment medicines and expect that our DUEXIS net sales will continue to decrease in future periods.

RAYOS. Net sales decreased \$14.9 million, or 21%, to \$56.9 million during the year ended December 31, 2021, from \$71.8 million during the year ended December 31, 2020. Net sales decreased by approximately \$11.4 million due to lower sales volume and \$3.5 million resulting from lower net pricing.

We have an exclusive license to U.S. patents and patent applications from Vectura covering RAYOS. Under our settlement agreement with Teva Pharmaceuticals Industries Limited (formerly known as Actavis Laboratories FL, Inc., which itself was formerly known as Watson Laboratories, Inc. – Florida), or Teva, Teva may enter the market on December 23, 2022, or earlier under certain circumstances. As a result, we expect our net sales for RAYOS to decline in future periods.

VIMOVO. Net sales decreased \$29.2 million, or 78%, to \$8.4 million during the year ended December 31, 2021, from \$37.6 million during the year ended December 31, 2020. Net sales decreased by approximately \$24.8 million due to lower sales volume as a result of generic competition which began in 2020 and \$4.4 million due to lower net pricing.

The table below reconciles our gross to net sales for the years ended December 31, 2021 and 2020 (in millions, except percentages):

	Year Ended December 31, 2021		Year Ended December 31, 2020	
	Amount	% of Gross Sales	Amount	% of Gross Sales
Gross sales	\$ 4,903.6	100%	\$ 4,039.4	100%
Adjustments to gross sales:				
Prompt pay discounts	(46.0)	(0.9)%	(52.3)	(1.3)%
Medicine returns	(17.6)	(0.4)%	(16.4)	(0.4)%
Co-pay and other patient assistance	(599.9)	(12.2)%	(877.3)	(21.7)%
Commercial rebates and wholesaler fees	(278.8)	(5.7)%	(304.2)	(7.5)%
Government rebates and chargebacks	(734.9)	(15.0)%	(588.8)	(14.6)%
Total adjustments	(1,677.2)	(34.2)%	(1,839.0)	(45.5)%
Net sales	\$ 3,226.4	65.8%	\$ 2,200.4	54.5%

During the year ended December 31, 2021, co-pay and other patient assistance costs, as a percentage of gross sales, decreased to 12.2% from 21.7% during the year ended December 31, 2020, primarily due to a decreased proportion of inflammation segment medicines sold, including the impact of generic competition on DUEXIS and VIMOVO sales.

On a quarter-to-quarter basis, our net sales have traditionally been lower in first half of the year, particularly in the first quarter, with the second half of the year representing a greater share of overall net sales each year. This is due to annual managed care plan changes and the re-setting of patients' medical insurance deductibles at the beginning of each year, resulting in higher co-pay and other patient assistance costs as patients meet their annual medical insurance deductibles during the first and second quarters, and higher net sales in the second half of the year after patients meet their deductibles and healthcare plans reimburse a greater portion of the total cost of our medicines.

Cost of Goods Sold. Cost of goods sold increased \$261.8 million to \$794.5 million during the year ended December 31, 2021, from \$532.7 million during the year ended December 31, 2020. The increase in cost of goods sold during the year ended December 31, 2021, compared to during the year ended December 31, 2020, was primarily due to an increase in sales volumes, an increase in royalty expense, an increase in amortization expense and the recording of inventory step-up expense during the year ended December 31, 2021. Royalty expense increased by \$112.9 million primarily due to royalties payable on net sales of TEPEZZA, which increased significantly during the year ended December 31, 2021 compared to the year ended December 31, 2020. Amortization expense increased \$80.5 million primarily due to the acquisition of the UPLIZNA developed technology intangible asset in the first quarter of 2021 and we recorded inventory step-up expense of \$27.6 million related to UPLIZNA based on the acquired units of inventory sold during the year ended December 31, 2021. In addition, we recorded a \$8.7 million DUEXIS inventory reserve due to the impact of generic competition on DUEXIS sales. As a percentage of net sales, cost of goods sold was 25% during the year ended December 31, 2021, compared to 24% during the year ended December 31, 2020. The increase in cost of goods sold as a percentage of net sales was primarily due to a change in the mix of medicines sold.

Research and Development Expenses. R&D expenses increased \$222.6 million to \$432.0 million during the year ended December 31, 2021, from \$209.4 million during the year ended December 31, 2020. The increase during the year ended December 31, 2021 compared to the year ended December 31, 2020, was primarily attributable to a \$136.1 million increase in clinical trial and manufacturing development costs reflecting increased activity in our R&D pipeline as well as the addition of our medicine candidates and development programs following the acquisition of Viela in March 2021 and an increase of \$59.1 million in employee-related costs. In addition, during the year ended December 31, 2021, we recognized \$40.0 million of an upfront cash payment in relation to our agreement with Arrowhead and \$28.1 million of an upfront payment and premium paid for shares of Alpine's common stock in relation to our agreement with Alpine. This was partially offset by the \$45.0 million upfront payment for the acquisition of Curzion, which was expensed as in-process research and development, or IPR&D, during the year ended December 31, 2020.

We expect our R&D expenses to increase significantly in future periods as a result of our on-going and planned clinical trials for our pipeline including new medicine candidates and development programs acquired in 2021.

Selling, General and Administrative Expenses. Selling, general and administrative expenses increased \$473.2 million to \$1,446.4 million during the year ended December 31, 2021, from \$973.2 million during the year ended December 31, 2020. The increase was primarily attributable to costs associated with the Viela acquisition in March 2021 and an increase in TEPEZZA commercial activities. These include an increase of \$150.9 million in employee-related costs, an increase of \$194.8 million in marketing program costs and an increase of \$57.4 million in consulting costs, primarily related to the integration of Viela. In addition, \$28.6 million of transaction costs were incurred during the year ended December 31, 2021 relating to the Viela acquisition.

We expect our selling, general and administrative expenses to increase significantly in future periods primarily due to continued support for our U.S. commercial and field-based organization and global expansion activities.

Impairment of long-lived asset. During the year ended December 31, 2021, we recorded an impairment charge of \$12.4 million as a result of vacating the Lake Forest office. Refer to Note 14, *Lease Obligations*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K, for further details.

Gain on sale of assets. During the year ended December 31, 2021, gain on sale of assets represents a \$2.0 million contingent consideration payment related to the sale of MIGERGOT in 2019.

During the year ended December 31, 2020, we completed the sale of rights to RAVICTI and BUPHENYL in Japan for cash proceeds of \$5.4 million, and we recorded a gain of \$4.9 million on the sale.

Interest Expense, Net. Interest expense, net, increased \$21.5 million to \$81.1 million during the year ended December 31, 2021, from \$59.6 million during the year ended December 31, 2020. The increase was primarily due to an increase in interest expense of \$17.8 million, primarily related to an additional \$1.6 billion aggregate principal amount of term loans borrowed pursuant to an amendment to our Credit Agreement and a decrease in interest income of \$3.7 million. Refer to Note 13, *Debt Agreements*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K, for further details.

Loss on Debt Extinguishment. During the year ended December 31, 2020, we recorded a loss on debt extinguishment of \$31.9 million in the consolidated statements of comprehensive income, which reflects the exchange of our 2.5% Exchangeable Senior Notes due 2022, or the Exchangeable Senior Notes. During the year ended December 31, 2020, \$400.0 million in aggregate principal amount of Exchangeable Senior Notes were exchanged for ordinary shares and cash payments.

(Benefit) Expense for Income Taxes. During the year ended December 31, 2021, we recorded a benefit for income taxes of \$71.7 million and an expense for income taxes of \$11.8 million during the year ended December 31, 2020. The benefit for income taxes recorded during the year ended December 31, 2021 resulted primarily from tax expense on pre-tax income and losses at the Irish statutory tax rate of \$57.9 million as offset by tax benefits recognized on share-based compensation of \$71.2 million and a tax benefit of \$49.4 million recognized due to a reduction in the state tax rate expected to apply to the reversal of temporary differences between the book values and tax bases of certain assets acquired through the Viela acquisition. A tax benefit of \$44.7 million was recognized on the pre-tax income and losses generated in jurisdictions with statutory tax rates different than the Irish statutory tax rate, a \$13.9 million tax benefit was recognized on intercompany inventory transfers and \$11.6 million of U.S. Federal and state tax credits were generated during the year. These tax benefits were partially offset by a tax expense of \$47.1 million attributable to disallowed officers' compensation under Section 162(m) of the Internal Revenue Code of 1986, as amended, or the Code and a tax expense of \$18.7 million generated from an intercompany transfer and license of intellectual property from a U.S. subsidiary to an Irish subsidiary.

The expense for income taxes recorded during the year ended December 31, 2020 was primarily attributable to a \$15.2 million provision recorded following the publication, on April 8, 2020, by the U.S. Department of the Treasury, of Final Regulations for Section 267A, or commonly referred to as the Anti-Hybrid Rules. The Final Regulations for Section 267A permanently disallow for U.S. tax purposes certain interest expense accrued to a foreign related party during the year ended December 31, 2019. As a result, we recorded a write off of a deferred tax asset related to this interest expense during the year ended December 31, 2020 and recognized a corresponding tax provision of \$15.2 million. The remainder of the expense for income taxes recorded during the year ended December 31, 2020 was primarily attributable to disallowed officers' compensation under Section 162(m) of the Code of \$14.6 million, disallowed in-process research and development expense incurred in connection with the Curzion acquisition of \$9.5 million and tax expense recognized on U.S. taxable income generated from an intercompany transfer of intellectual property from a U.S. subsidiary to an Irish subsidiary during the year ended December 31, 2020 of \$11.2 million and changes in valuation allowances of \$4.2 million. These expenses were partially offset by tax benefits recognized on share-based compensation of \$23.8 million, additional U.S. Federal and state tax credits of \$13.8 million and the recognition of a deferred tax asset in the Irish subsidiary resulting from the intercompany transfer of intellectual property of \$6.0 million.

Information by Segment

Refer to Note 11, *Segment and Other Information*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K for a reconciliation of our segment operating income to our total income before (benefit) expense for income taxes for the years ended December 31, 2021 and 2020.

Orphan Segment

The following table reflects our orphan segment net sales and segment operating income for the years ended December 31, 2021 and 2020 (in thousands, except percentages).

	For the Year Ended December 31,		Change	% Change
	2021	2020		
Net sales	\$ 2,895,518	\$ 1,787,655	\$ 1,107,863	62%
Segment operating income	1,219,317	783,560	435,757	56%

Net sales. The increase in orphan segment net sales during the year ended December 31, 2021 is described in the *Consolidated Results* section above.

Segment operating income. Orphan segment operating income increased \$435.7 million to \$1,219.3 million during the year ended December 31, 2021, from \$783.6 million during the year ended December 31, 2020. The increase was primarily attributable to an increase in net sales of \$1,107.9 million as described above, partially offset by an increase in selling, general and administrative expenses of \$353.0 million, an increase in R&D expenses of \$168.5 million and an increase of \$126.0 million in royalty expense primarily related to an increase in royalties payable on net sales of TEPEZZA during the year ended December 31, 2021 compared to the year ended December 31, 2020. The increase in selling, general and administrative expenses was mainly due to an increase in the commercial and field-based organization for TEPEZZA, and the increase in R&D expenses was primarily due to incremental net operating expense of Viela after we acquired it on March 15, 2021.

Inflammation Segment

The following table reflects our inflammation segment net sales and segment operating income for the years ended December 31, 2021 and 2020 (in thousands, except percentages).

	For the Year Ended December 31,		Change	% Change
	2021	2020		
Net sales	\$ 330,892	\$ 412,774	\$ (81,882)	(20)%
Segment operating income	156,197	212,061	(55,864)	(26)%

Net sales. The decrease in inflammation segment net sales during the year ended December 31, 2021 is described in the *Consolidated Results* section above.

Segment operating income. Inflammation segment operating income decreased \$55.9 million to \$156.2 million during the year ended December 31, 2021, from \$212.1 million during the year ended December 31, 2020. The decrease was primarily attributable to a decrease in net sales of \$81.9 million as described above and a \$8.7 million inventory reserve for DUEXIS due to the impact of generic competition on DUEXIS sales, partially offset by a decrease in selling, general and administrative expenses of \$26.9 million.

Non-GAAP Financial Measures

EBITDA, or earnings before interest, taxes, depreciation and amortization, adjusted EBITDA, non-GAAP net income and non-GAAP earnings per share are used and provided by us as non-GAAP financial measures. These non-GAAP financial measures are intended to provide additional information on our performance, operations and profitability. Adjustments to our GAAP figures as well as EBITDA exclude acquisition/divestiture-related costs, manufacturing plant start-up costs, drug substance harmonization costs, fees related to refinancing activities, restructuring and realignment costs and litigation settlements, as well as non-cash items such as share-based compensation, inventory step-up expense, depreciation and amortization, non-cash interest expense, long-lived assets impairment charges, loss on debt extinguishments, gain on sale of assets, gain on equity security investments and other non-cash adjustments. Certain other special items or substantive events may also be included in the non-GAAP adjustments periodically when their magnitude is significant within the periods incurred. We maintain an established non-GAAP cost policy that guides the determination of what costs will be excluded in non-GAAP measures. We believe that these non-GAAP financial measures, when considered together with the GAAP figures, can enhance an overall understanding of our financial and operating performance. The non-GAAP financial measures are included with the intent of providing investors with a more complete understanding of our historical financial results and trends and to facilitate comparisons between periods. In addition, these non-GAAP financial measures are among the indicators our management uses for planning and forecasting purposes and measuring our performance. These non-GAAP financial measures should be considered in addition to, and not as a substitute for, or superior to, financial measures calculated in accordance with GAAP. The non-GAAP financial measures used by us may be calculated differently from, and therefore may not be comparable to, non-GAAP financial measures used by other companies.

Beginning in the fourth quarter of 2021, following consultation with the staff of the Division of Corporation Finance of the U.S. Securities and Exchange Commission, we no longer exclude upfront and milestone payments related to license and collaboration agreements from our non-GAAP financial measures and its line-item components. For purposes of comparability, non-GAAP financial measures for the year ended December 31, 2020 and 2019 have been updated to reflect this change. The upfront and milestone payments related to license and collaboration agreements continue to be excluded from our segment operating income and from certain measures contained in our credit agreement that are relevant to, among other things, the calculation of the interest rate.

Reconciliations of reported GAAP net income to EBITDA, adjusted EBITDA and non-GAAP net income, and the related per share amounts, were as follows (in thousands, except share and per share amounts):

	For the Years Ended December 31,	
	2021	2020
GAAP net income	\$ 534,491	\$ 389,796
Depreciation ⁽¹⁾	17,475	24,303
Amortization and step-up:		
Intangible amortization expense ⁽²⁾	336,277	255,148
Inventory step-up expense ⁽³⁾	27,572	—
Interest expense, net (including amortization of debt discount and deferred financing costs)	81,063	59,616
(Benefit) expense for income taxes	(71,664)	11,849
EBITDA	925,214	740,712
Other non-GAAP adjustments:		
Share-based compensation ⁽⁴⁾	219,086	146,627
Acquisition/divestiture-related costs ⁽⁵⁾	95,929	49,196
Restructuring and realignment costs ⁽⁶⁾	26,309	(141)
Impairment of long-lived assets ⁽⁷⁾	12,371	1,713
Litigation settlements ⁽⁸⁾	5,000	—
Manufacturing plant start-up costs ⁽⁹⁾	3,622	—
Fees related to refinancing activities ⁽¹⁰⁾	—	54
Loss on debt extinguishment ⁽¹¹⁾	—	31,856
Drug substance harmonization costs ⁽¹²⁾	—	542
Gain on equity security investments ⁽¹³⁾	(1,257)	—
Gain on sale of assets ⁽¹⁴⁾	(2,000)	(4,883)
Total of other non-GAAP adjustments ⁽¹⁹⁾	359,060	224,964
Adjusted EBITDA ⁽¹⁹⁾	\$ 1,284,274	\$ 965,676

For the Years Ended December 31,

	2021	2020
GAAP net income	\$ 534,491	\$ 389,796
Non-GAAP adjustments:		
Depreciation ⁽¹⁾	17,475	24,303
Amortization and step-up:		
Intangible amortization expense ⁽²⁾	336,277	255,148
Inventory step-up expense ⁽³⁾	27,572	—
Amortization of debt discount and deferred financing costs ⁽¹⁵⁾	5,189	12,640
Share-based compensation ⁽⁴⁾	219,086	146,627
Acquisition/divestiture-related costs ⁽⁵⁾	95,929	49,196
Restructuring and realignment costs ⁽⁶⁾	26,309	(141)
Impairment of long-lived assets ⁽⁷⁾	12,371	1,713
Litigation settlements ⁽⁸⁾	5,000	—
Manufacturing plant start-up costs ⁽⁹⁾	3,622	—
Fees related to refinancing activities ⁽¹⁰⁾	—	54
Loss on debt extinguishment ⁽¹¹⁾	—	31,856
Drug substance harmonization costs ⁽¹²⁾	—	542
Gain on equity security investments ⁽¹³⁾	(1,257)	—
Gain on sale of assets ⁽¹⁴⁾	(2,000)	(4,883)
Total pre-tax non-GAAP adjustments ⁽¹⁹⁾	745,573	517,055
Income tax effect of pre-tax non-GAAP adjustments ⁽¹⁶⁾	(169,554)	(98,628)
Other non-GAAP income tax adjustments ⁽¹⁷⁾	(20,800)	20,541
Total non-GAAP adjustments ⁽¹⁹⁾	555,219	438,968
Non-GAAP Net Income ⁽¹⁹⁾	\$ 1,089,710	\$ 828,764
Non-GAAP Earnings Per Share:		
Weighted average ordinary shares – Basic	225,551,410	203,967,246
Non-GAAP Earnings Per Share – Basic		
GAAP earnings per share - Basic	\$ 2.37	\$ 1.91
Non-GAAP adjustments ⁽¹⁹⁾	2.46	2.15
Non-GAAP earnings per share – Basic ⁽¹⁹⁾	\$ 4.83	\$ 4.06
Non-GAAP net income ⁽¹⁹⁾	\$ 1,089,710	\$ 828,764
Effect of assumed conversion of Exchangeable Senior Notes, net of tax ⁽¹⁸⁾	—	3,789
Numerator - non-GAAP net income ⁽¹⁹⁾	\$ 1,089,710	\$ 832,553
Weighted average ordinary shares – Diluted		
Weighted average ordinary shares – Basic	225,551,410	203,967,246
Ordinary share equivalents	10,129,073	18,203,897
Denominator - weighted average ordinary shares – Diluted	235,680,483	222,171,143
Non-GAAP Earnings Per Share – Diluted		
GAAP earnings per share – Diluted	\$ 2.27	\$ 1.81
Non-GAAP adjustments ⁽¹⁹⁾	2.35	1.94
Non-GAAP earnings per share – Diluted ⁽¹⁹⁾	\$ 4.62	\$ 3.75

(1) Represents depreciation expense related to our property, plant, equipment, software and leasehold improvements.

(2) Intangible amortization expenses are primarily associated with our intellectual property rights, developed technology and customer relationships related to TEPEZZA, KRYSTEXXA, RAVICTI, PROCYSBI, ACTIMMUNE, UPLIZNA, BUPHENYL, PENNSAID 2% and RAYOS.

- (3) During the year ended December 31, 2021, we recognized in cost of goods sold \$27.6 million for inventory step-up expense related to UPLIZNA inventory revalued in connection with the Viela acquisition. Refer to Note 5, *Inventories*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K for further detail.
- (4) Represents share-based compensation expense associated with our stock option, restricted stock unit and performance stock unit grants to our employees and non-employee directors and our employee share purchase plan.
- (5) Primarily represents transaction and integration costs, including, advisory, legal, consulting and certain employee-related costs, incurred in connection with our acquisitions and divestitures. Costs recovered from subleases of acquired facilities and reimbursed expenses incurred under transition arrangements for divestitures are also reflected in this line item. In addition, the year ended December 31, 2020 amounts include the Curzion acquisition payment of \$45.0 million, which was recorded as a R&D expense.
- (6) Since 2020, we have been working to expand our TEPEZZA drug substance manufacturing capacity in the external Copenhagen, Denmark, Boulder, Colorado, and Seattle, Washington facilities. During the fourth quarter of 2021, we ended further TEPEZZA drug substance manufacturing development activities in the Seattle facility and recorded a charge of \$16.6 million to R&D expense related to manufacturing development activities in this facility. We expect existing and planned future production capacity at the Copenhagen and Boulder facilities to produce sufficient TEPEZZA drug substance to meet our future needs. In addition, rent and maintenance charges of \$9.7 million were recorded for the leased Lake Forest office that we vacated in the first quarter of 2021.
- (7) During the year ended December 31, 2021, we recorded a right-of-use asset impairment charge of \$12.4 million as a result of vacating the leased Lake Forest office.

During the year ended December 31, 2020, we recorded an impairment charge of \$1.7 million related to the Novato, California office lease, which was assumed through an acquisition.

- (8) We recorded \$5.0 million of expense during the year ended December 31, 2021 for litigation settlements.
- (9) During the year ended December 31, 2021, we recorded \$3.6 million of manufacturing plant start-up costs related to the purchase of a biologic drug product manufacturing facility from EirGen in July 2021.
- (10) Represents arrangement and other fees relating to our refinancing activities.
- (11) During the year ended December 31, 2020, we recorded a loss on debt extinguishment of \$31.9 million in the consolidated statements of comprehensive income, which reflects the extinguishment of our Exchangeable Senior Notes.
- (12) During the year ended December 31, 2016, we entered into a definitive agreement to acquire certain rights to interferon gamma-1b, marketed as IMUKIN in an estimated thirty countries primarily in Europe and the Middle East, or the IMUKIN purchase agreement. We already owned the rights to interferon gamma-1b marketed as ACTIMMUNE in the United States, Canada and Japan. In connection with the IMUKIN purchase agreement, we also committed to pay our contract manufacturer certain amounts related to the harmonization of the manufacturing processes for ACTIMMUNE and IMUKIN drug substance, or the harmonization program. At the time we entered into the IMUKIN purchase agreement and the harmonization program commitment was made, we had anticipated achieving certain benefits should the Phase 3 clinical trial evaluating ACTIMMUNE for the treatment of Friedreich's ataxia be successful. If the study had been successful and if U.S. marketing approval had subsequently been obtained, we had forecasted significant increases in demand for the medicine and the harmonization program would have resulted in significant benefits to us. Following our discontinuation of the Friedreich's ataxia program, we determined that certain assets, including an upfront payment related to the IMUKIN purchase agreement, were impaired, and the costs under the harmonization program would no longer have benefit to us and should be expensed as incurred.
- (13) We held investments in equity securities with readily determinable fair values of \$13.2 million as of December 31, 2021 which are included in other assets in the consolidated balance sheet. For the year ended December 31, 2021, we recognized net unrealized gains of \$1.3 million due to the change in fair value of these securities.

(14) Gain on sale of assets during the year ended December 31, 2021, represents a \$2.0 million contingent consideration payment related to the sale of MIGERGOT in 2019.

During the year ended December 31, 2020, we completed the sale of rights to RAVICTI and BUPHENYL in Japan for cash proceeds of \$5.4 million, and we recorded a gain of \$4.9 million on the sale.

(15) Represents amortization of debt discount and deferred financing costs associated with our debt.

(16) Income tax adjustments on pre-tax non-GAAP adjustments represent the estimated income tax impact of each pre-tax non-GAAP adjustment based on the statutory income tax rate of the applicable jurisdictions for each non-GAAP adjustment.

(17) During the year ended December 31, 2021, we recognized a U.S. federal and state tax liability on U.S. taxable income generated from an intercompany transfer and license of intellectual property from a U.S. subsidiary to an Irish subsidiary which was partially offset by the recognition of a deferred tax asset in the Irish subsidiary, resulting in a non-GAAP tax adjustment of \$28.3 million. We also recognized a reduction in the state tax rate expected to apply to the reversal of temporary differences between the book values and tax bases of certain assets acquired through the Viela acquisition. The reduction in state tax rate resulted in a reduction in the deferred tax liability relating to these assets and a non-GAAP tax adjustment of \$49.1 million.

During the year ended December 31, 2020, following the publication by the United States Department of Treasury and the Internal Revenue Service of the Final Regulations on the Anti-Hybrid Rules on April 8, 2020, we recorded a write-off of a deferred tax asset related to certain interest expense accrued to a foreign related party during the year ended December 31, 2019 and recognized a corresponding one-time tax provision, resulting in a non-GAAP tax adjustment of \$15.2 million. We also recognized a U.S. federal tax liability on U.S. taxable income generated from an intercompany transfer of intellectual property from a U.S. subsidiary to an Irish subsidiary, which was partially offset by the recognition of a deferred tax asset in the Irish subsidiary, resulting in a non-GAAP tax adjustment of \$5.3 million.

(18) During the year ended December 31, 2020, \$400.0 million in aggregate principal amount of Exchangeable Senior Notes were fully extinguished and exchanged for ordinary shares or cash.

(19) As discussed above, following consultation with the staff of the Division of Corporation Finance of the U.S. Securities and Exchange Commission, we no longer exclude upfront and milestone payments related to license and collaboration agreements from our non-GAAP financial measures and its line-item components. Adjusted EBITDA and non-GAAP net income for the years ended December 31, 2021 and 2020, includes \$89.7 million and \$33.0 million of upfront and milestone payments related to license and collaboration agreements, respectively. These amounts continue to be excluded from our segment operating income and from certain measures contained in our credit agreement that are relevant to, among other things, the calculation of the interest rate.

Liquidity, Financial Position and Capital Resources

As of December 31, 2021, we had retained earnings of \$318.6 million. We expect that our sales and marketing expenses will continue to increase as a result of the commercialization of our medicines and global expansion initiatives, but we believe these cost increases will be more than offset by higher net sales and gross profits in future periods. Additionally, we expect that our R&D costs will increase as we acquire or develop more development-stage medicine candidates and advance our candidates through the clinical development and regulatory approval processes. In particular, we expect to incur substantial costs in connection with advancing our pipeline of medicine candidates and development programs in on-going and planned clinical trials.

Following the highly successful launch of TEPEZZA, which significantly exceeded our expectations, we are in the process of expanding our production capacity to meet anticipated future demand for TEPEZZA. As of December 31, 2021, we had total purchase commitments, including the minimum annual order quantities and binding firm orders, with AGC Biologics A/S (formerly known as CMC Biologics A/S) for TEPEZZA drug substance of €122.8 million (\$139.2 million converted at a Euro-to-Dollar exchange rate as of December 31, 2021 of 1.1338), to be delivered through December 2024.

We also expect to incur additional costs and to enter into additional purchase commitments in connection with our efforts to expand TEPEZZA production capacity in order to meet anticipated increases in demand.

In July 2021, we completed the purchase of a biologic drug product manufacturing facility from EirGen for \$67.9 million. Refer to Note 4, *Acquisitions, Divestitures and other Arrangements*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K, for further details. We expect to incur approximately \$35.0 million in capital expenditures through 2022 in order to complete the drug product facility.

In February 2020, we purchased a three-building campus in Deerfield, Illinois, for total consideration and directly attributable transaction costs of \$118.5 million. The Deerfield campus totals 70 acres and consists of approximately 650,000 square feet of office space. We made significant capital expenditures during the first quarter of 2021 in order to prepare the Deerfield campus for occupancy. Our office employees previously located in Lake Forest, Illinois moved to the Deerfield campus in February 2021. Vacating the Lake Forest leased office building in February 2021 represented a triggering event for impairment consideration of the right-of-use asset relating to this building. During the first quarter of 2021, we recorded an impairment charge of \$12.4 million as a result of vacating the Lake Forest office. This charge was reported within impairment of long-lived asset in the consolidated statement of comprehensive income. In addition, we recorded a liability of \$5.6 million during the year ended December 31, 2021 for maintenance charges as a result of vacating the leased Lake Forest office. In January 2022, we entered a sublease agreement for the entire Lake Forest office building for the remaining term of the original lease through March 31, 2031.

During the first quarter of 2021, under our license agreement with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., or together referred to as Roche, we made a milestone payment of CHF50.0 million (\$56.1 million when converted using a CHF-to-Dollar exchange rate at the date of payment of 1.1228) in relation to the attainment of TEPEZZA net sales milestones. The liability for this milestone payment was recorded during the year ended December 31, 2020. In April 2021, under the acquisition agreement for River Vision Development Corp., or River Vision, we made a TEPEZZA net sales milestone payment of \$67.0 million. The liability for this milestone payment was recorded during the year ended December 31, 2020. There are no further TEPEZZA net sales milestone obligations remaining to Roche and the former River Vision stockholders. Our remaining obligation to Roche relating to the attainment of various TEPEZZA development and regulatory milestones is CHF43.0 million (\$47.0 million when converted using a CHF-to-Dollar exchange rate at December 31, 2021 of 1.0937).

During the year ended December 31, 2020, we committed to invest as a strategic limited partner in four venture capital funds: Forbion Growth Opportunities Fund I C.V., Forbion Capital Fund V C.V., Aisling Capital V, L.P. and RiverVest Venture Fund V, L.P. As of December 31, 2021, the total carrying amount of our investments in these funds was \$22.6 million, which is included in other assets in the consolidated balance sheet, and our total future commitments to these funds are \$42.3 million.

We have financed our operations to date through equity financings, debt financings and the issuance of convertible notes, along with cash flows from operations during the last several years. As of December 31, 2021, we had \$1.6 billion in cash and cash equivalents and total debt with a book value of \$2.6 billion and face value of \$2.6 billion. We believe our existing cash and cash equivalents and our expected cash flows from our operations will be sufficient to fund our business needs for at least the next 12 months from the issuance of the financial statements in this Annual Report on Form 10-K. We do not have any financial or non-financial covenants that we expect to be affected by the economic disruptions and negative effects of the COVID-19 pandemic.

We have a significant amount of debt outstanding on a consolidated basis. For a description of our debt agreements, refer to Note 13, *Debt Agreements*, of the Notes to Consolidated Financial Statements, included in Item 15 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: making it more difficult for us to satisfy our obligations; requiring a substantial portion of our cash flows from operations to be dedicated to the payment of principal and interest on our indebtedness, therefore reducing our ability to use our cash flows to fund acquisitions, capital expenditures, R&D and future business opportunities; limiting our ability to obtain additional financing, including borrowing additional funds; increasing our vulnerability to, and reducing our flexibility to respond to, general adverse economic and industry conditions; limiting our flexibility in planning for, or reacting to, changes in our business and the industry in which we operate; and placing us at a disadvantage as compared to our competitors, to the extent that they are not as highly leveraged. We may not be able to generate sufficient cash to service all of our indebtedness and may be forced to take other actions to satisfy our obligations under our indebtedness.

In addition, the indenture governing our 5.5% Senior Notes due 2027 and our Credit Agreement impose various covenants that limit our ability and/or our restricted subsidiaries' ability to, among other things, pay dividends or distributions, repurchase equity, prepay junior debt and make certain investments, incur additional debt and issue certain preferred stock, incur liens on assets, engage in certain asset sales or merger transactions, enter into transactions with affiliates, designate subsidiaries as unrestricted subsidiaries; and allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to us.

During the year ended December 31, 2021, we issued an aggregate of 6.0 million ordinary shares in connection with stock option exercises and the vesting of restricted stock units and performance stock units and employee share purchase plan purchases. We received a total of \$73.1 million in net proceeds in connection with such issuances. During the year ended December 31, 2021, we made payments of \$166.0 million for employee withholding taxes relating to vesting of share-based awards.

Since our inception, we have not engaged in any off-balance sheet arrangements, including the use of structured finance, special purpose entities or variable interest entities, other than the indemnification agreements discussed in Note 15, *Commitments and Contingencies*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K.

Sources and Uses of Cash

The following table provides a summary of our cash position and cash flows for the years ended December 31, 2021 and 2020 (in thousands):

	<u>For the Years Ended December 31,</u>	
	<u>2021</u>	<u>2020</u>
Cash, cash equivalents and restricted cash	\$ 1,584,156	\$ 2,083,479
Cash provided by (used in):		
Operating activities	1,035,271	555,688
Investing activities	(2,994,111)	(464,071)
Financing activities	1,470,123	904,579

Operating Cash Flows

Net cash provided by operating activities during the year ended December 31, 2021 of \$1,035.3 million was primarily attributable to cash collections from gross sales, partially offset by payments made related to patient assistance costs for our medicines and government rebates for our orphan segment medicines, payments related to selling, general and administrative expenses, including transaction costs related to the Viela acquisition, and payments related to R&D expenses.

Net cash provided by operating activities during the year ended December 31, 2020 of \$555.7 million was primarily attributable to cash collections from gross sales, partially offset by payments made related to patient assistance costs for our inflammation segment medicines and government rebates for our orphan segment medicines, payments related to selling, general and administrative expenses and R&D expenses and advanced payments for TEPEZZA inventory.

Investing Cash Flows

Net cash used in investing activities of \$2,994.1 million during the year ended December 31, 2021 was primarily attributable to payments for acquisitions, net of \$2,845.3 million which was primarily attributable to \$2.6 billion paid in relation to the Viela acquisition, net of acquired cash. In addition, we made a milestone payment of CHF50.0 million (\$56.1 million when converted using a CHF-to-Dollar exchange rate at the date of payment of 1.1228) under our license agreement with Roche and we made a milestone payment of \$67.0 million to the former River Vision stockholders during the year ended December 31, 2021. In the third quarter of 2021, we completed the purchase of a biologic drug product manufacturing facility from EirGen for \$67.9 million, which included an upfront cash payment of \$64.8 million and \$3.1 million of additional transaction costs, legal fees and liabilities assumed and we paid an upfront cash payment of \$40.0 million in relation to the global agreement with Arrowhead in July 2021.

Net cash used in investing activities during the year ended December 31, 2020 of \$464.1 million was primarily attributable to payments for acquisitions of \$262.3 million which consisted of \$215.2 million of milestone payments associated with the acquisition of River Vision and our agreements with Roche, with S.R. One, Limited and with Lundbeckfond Invest A/S, and \$45.0 million due to the acquisition of Curzion in the second quarter of 2020. Additionally, \$112.5 million was paid in the first quarter of 2020 in relation to the purchase of a three-building campus in Deerfield, Illinois. We also paid an upfront cash payment of \$30.0 million in the fourth quarter of 2020 related to a global agreement entered into with Halozyme, that gives us exclusive access to Halozyme's ENHANZE drug delivery technology for subcutaneous formulation of medicines targeting IGF-1R. We intend to use ENHANZE to develop a subcutaneous formulation of TEPEZZA.

Financing Cash Flows

Net cash provided by financing activities during the year ended December 31, 2021 of \$1,470.1 million was primarily attributable to an additional \$1.6 billion aggregate principal amount of term loans borrowed pursuant to an amendment to our Credit Agreement, the proceeds of which, in addition to a portion of our existing cash on hand, was used to pay the consideration for the Viela acquisition, partially offset by \$166.0 million payment of employee withholding taxes relating to share-based awards.

Net cash provided by financing activities during the year ended December 31, 2020 of \$904.6 million was primarily attributable to the issuance of 13.6 million ordinary shares in connection with our underwritten public equity offering in August 2020. We received net proceeds of approximately \$919.8 million after deducting underwriting discounts and other offering expenses payable by us in connection with such offering.

Financial Condition as of December 31, 2021 compared to December 31, 2020

Inventories, net. Inventories, net, increased \$150.4 million, from \$75.3 million as of December 31, 2020 to \$225.7 million as of December 31, 2021. The increase was primarily due to stepped-up UPLIZNA inventory of \$151.6 million, which consisted of \$120.9 million of stepped-up work in process, \$20.6 million of stepped-up finished goods and \$10.1 million stepped-up raw materials. We recorded \$27.6 million of UPLIZNA inventory step-up expense in cost of goods sold during the year ended December 31, 2021.

Prepaid expenses and other current assets. Prepaid expenses and other current assets increased \$105.2 million, from \$251.9 million as of December 31, 2020 to \$357.1 million as of December 31, 2021. The increase was primarily due to an increase of \$36.3 million in prepaid income taxes and income taxes receivable, an increase of \$22.4 million in upfront payments for inventory and an increase of \$13.9 million in deferred charge for taxes on intercompany profits.

Property, plant and equipment, net. Property, plant and equipment, net, increased \$103.3 million, from \$189.0 million as of December 31, 2020 to \$292.3 million as of December 31, 2021. The increase was primarily due to additions of \$46.2 million related to the purchase of a biologic drug product manufacturing facility from EirGen in July 2021 and \$45.9 million of additions related to the Deerfield campus. Refer to Note 4, *Acquisitions, Divestitures and other Arrangements*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K for further details of the purchase of the biologic drug product manufacturing facility. We expect to incur approximately \$35.0 million in capital expenditures through 2022 in order to complete the drug product facility.

Developed technology and other intangible assets, net. Developed technology and other intangible assets, net, increased \$1,177.2 million, from \$1,782.9 million as of December 31, 2020 to \$2,960.1 million as of December 31, 2021. During the year ended December 31, 2021, in connection with the acquisition of Viela, we capitalized \$1,493.0 million of developed technology related to UPLIZNA. This was partially offset by amortization of developed technology of \$336.3 million during the year ended December 31, 2021.

In-process research and development. On March 15, 2021, we completed the acquisition of Viela and acquired \$910.0 million of IPR&D. On March 23, 2021, our strategic partner, Mitsubishi Tanabe Pharma Corporation, received manufacturing and marketing approval of UPLIZNA in Japan. As a result, we transferred \$30.0 million of IPR&D to developed technology. As of December 31, 2021, the remaining IPR&D relating to the Viela acquisition was \$880.0 million.

Goodwill. Goodwill increased \$653.0 million, from \$413.7 million as of December 31, 2020 to \$1,066.7 million as of December 31, 2021 due to the Viela acquisition. Refer to Note 4, *Acquisitions, Divestitures and other Arrangements*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K for further details of this acquisition.

Other assets. Other assets increased \$85.0 million, from \$55.7 million as of December 31, 2020 to \$140.7 million as of December 31, 2021. In October 2019, we entered into an agreement for lease relating to approximately 63,000 square feet of office space under construction in Dublin, Ireland. In May 2021, the construction of the office was completed by the lessor and the lease became effective. As a result, we recognized \$60.9 million as a right-of-use asset and a corresponding lease liability on the consolidated balance sheet.

Long-term debt, net. Long-term debt, net increased \$1,551.8 million from \$1,003.4 million as of December 31, 2020 to \$2,555.2 million as of December 31, 2021. The increase was primarily related to an additional \$1.6 billion aggregate principal amount of term loans we borrowed pursuant to an amendment to our Credit Agreement, the proceeds of which, in addition to a portion of our existing cash on hand, was used to pay the consideration for the Viela acquisition. Refer to Note 13, *Debt Agreements*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K.

Deferred tax liabilities, net. Deferred tax liabilities, net, increased \$324.0 million from \$66.5 million as of December 31, 2020 to \$390.5 million as of December 31, 2021 primarily due to the Viela acquisition. Refer to Note 4, *Acquisitions, Divestitures and other Arrangements*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K for further details of this acquisition.

Other long-term liabilities. Other long-term liabilities increased \$71.4 million, from \$101.7 million as of December 31, 2020 to \$173.1 million as of December 31, 2021. In October 2019, we entered into an agreement for lease relating to approximately 63,000 square feet of office space under construction in Dublin, Ireland. In May 2021, the construction of the office was completed by the lessor and the lease became effective. As a result, we recognized \$60.9 million as a right-of-use asset and a corresponding lease liability on the consolidated balance sheet.

Contractual Obligations

As of December 31, 2021, minimum future cash payments due under contractual obligations, including, among others, our debt agreements, purchase agreements with third-party manufacturers and non-cancelable lease agreements, were as follows (in thousands):

	2022	2023	2024	2025	2026	2027 & Thereafter	Total
Debt agreements – principal ⁽¹⁾	\$ 16,000	\$ 16,000	\$ 16,000	\$ 16,000	\$434,026	\$2,108,000	\$2,606,026
Debt agreements - interest ⁽¹⁾	83,853	98,198	111,594	110,750	99,392	90,144	593,931
Purchase commitments ⁽²⁾	130,520	55,652	14,302	5,000	5,000	—	210,474
Lease obligations ⁽³⁾	6,269	9,986	10,677	10,414	10,273	85,081	132,700
Total contractual cash obligations	\$236,642	\$179,836	\$152,573	\$142,164	\$548,691	\$2,283,225	\$3,543,131

(1) Represents the minimum contractual obligation due under the following debt agreements:

- \$1.6 billion under our term loans, which includes estimated monthly interest payments based on the applicable interest rate at December 31, 2021 of 2.25%, quarterly payments of 0.25% of the principal and repayment of the remaining principal in March 2028.
- \$418.0 million under our term loans, which includes estimated monthly interest payments based on the applicable interest rate at December 31, 2021 of 2.13% and repayment of the remaining principal in May 2026.
- \$600.0 million of our 5.5% Senior Notes due 2027, which includes bi-annual interest payments and repayment of the principal in August 2027.

(2) These amounts reflect the following purchase commitments with our third-party manufacturers. Refer to Note 15, *Commitments and Contingencies*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K for further details.

(3) These amounts reflect payments due under our leases, which are principally for our facilities. For further details regarding these properties, see Item 2 of Part I, *Properties*, of this Annual Report on Form 10-K. Our office employees previously located in Lake Forest, Illinois moved to the Deerfield campus in February 2021. In January 2022, we entered a sublease agreement for the entire Lake Forest office building for the remaining term of the original lease through March 31, 2031.

The above table does not include the following items:

- On December 15, 2021, we entered into an exclusive license agreement with Alpine for the development and commercialization of up to four preclinical candidates generated from Alpine's unique discovery platform. In connection with the execution of the license agreement, we entered into a stock purchase agreement with Alpine to purchase a minority stake of 951,980 shares of Alpine's common stock in a private placement. Under the terms of the agreements, we paid Alpine \$15.0 million in the fourth quarter of 2021 and paid \$25.0 million in the first quarter of 2022. In addition, Alpine is eligible to receive up to \$381.0 million per program, or approximately \$1.52 billion in total, in future success-based payments related to development, regulatory and commercial milestones, as well as tiered royalties from a mid-single digit percentage to a low double-digit percentage on global net sales. Refer to Note 4, *Acquisitions, Divestitures and other Arrangements*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K for further details.
- An agreement to lease entered into in November 2021 relating to approximately 192,000 square feet of office and laboratory space under construction in Rockville, Maryland. Lease commencement will begin when construction of the building is completed by the lessor and we have access to begin the construction of leasehold improvements. We expect to receive access to the office and laboratory space and commence the related lease in the first half of 2023 and incur leasehold improvement costs through 2024 in order to prepare the building for occupancy.
- Effective January 1, 2022, the South San Francisco, California office lease was amended to include an additional suite with approximately 20,000 square feet and the lease term on the existing lease was extended to December 31, 2031.
- On June 18, 2021, we entered into a global agreement with Arrowhead for ARO-XDH, a discovery-stage investigational RNA interference therapeutic, being developed by Arrowhead as a potential treatment for uncontrolled gout. Under the terms of the agreement, we paid Arrowhead an upfront cash payment of \$40.0 million in July 2021 and agreed to pay additional potential future milestone payments of up to \$660.0 million contingent on the achievement of certain development, regulatory and commercial milestones, and low to mid-teens royalties on worldwide calendar year net sales of licensed products. Refer to Note 4, *Acquisitions, Divestitures and other Arrangements*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K for further details.
- Non-cancellable advertising commitments due within one year of \$47.6 million, primarily related to agreements for advertising for TEPEZZA and KRYSTEXXA.
- As of December 31, 2021, our contingent liability for uncertain tax positions amounted to \$28.4 million (excluding interest and penalties). Due to the nature and timing of the ultimate outcome of these uncertain tax positions, we cannot make a reasonably reliable estimate of the amount and period of related future payments, if any. Therefore, our contingent liability has been excluded from the above contractual obligations table. We do not expect a significant tax payment related to these obligations within the next year.
- Assumed material obligations to make royalty and milestone payments to certain third parties on net sales of certain of our medicines. Refer to Note 15, *Commitments and Contingencies*, of the Notes to Consolidated Financial Statements, included in Item 15 of this Annual Report on Form 10-K for details of these material obligations.
- During the year ended December 31, 2020, we committed to invest as a strategic limited partner in four venture capital funds: Forbion Growth Opportunities Fund I C.V., Forbion Capital Fund V C.V., Aisling Capital V, L.P. and RiverVest Venture Fund V, L.P. As of December 31, 2021, the total carrying amount of our investments in these funds was \$22.6 million, which is included in other assets in the consolidated balance sheet, and includes \$12.7 million in net cash payments for investments made during the year ended December 31, 2021. As of December 31, 2021, our total future commitments to these funds were \$42.3 million.

CRITICAL ACCOUNTING POLICIES AND ESTIMATES

The methods, estimates and judgments that we use in applying our critical accounting policies have a significant impact on the results that we report in our financial statements. Some of our accounting policies require us to make difficult and subjective judgments, often as a result of the need to make estimates regarding matters that are inherently uncertain.

We have identified the accounting policies and estimates listed below as those that we believe require management's most subjective and complex judgments in estimating the effect of inherent uncertainties. This section should also be read in conjunction with Note 2, *Summary of Significant Accounting Policies*, of the Notes to our Consolidated Financial Statements included in Item 15 of this Annual Report on Form 10-K, which includes a discussion of these and other significant accounting policies.

Revenue Recognition

In the United States, we sell our medicines primarily to wholesale distributors, specialty distributors and specialty pharmacy providers. In other countries, we sell our medicines primarily to wholesale distributors and other third-party distribution partners. These customers subsequently resell our medicines to health care providers and patients. In addition, we enter into arrangements with health care providers and payers that provide for government-mandated or privately negotiated discounts and allowances related to our medicines. Revenue is recognized when performance obligations under the terms of a contract with a customer are satisfied. The majority of our contracts have a single performance obligation to transfer medicines. Accordingly, revenues from medicine sales are recognized when the customer obtains control of our medicines, which occurs at a point in time, typically upon delivery to the customer. Revenue is measured as the amount of consideration we expect to receive in exchange for transferring medicines and is generally based upon a list or fixed price less allowances for medicine returns, rebates and discounts. We sell our medicines to wholesale pharmaceutical distributors and pharmacies under agreements with payment terms typically less than 90 days. Our process for estimating reserves established for these variable consideration components does not differ materially from our historical practices.

Medicine Sales Discounts and Allowances

The nature of our contracts gives rise to variable consideration because of allowances for medicine returns, rebates and discounts. Allowances for medicine returns, rebates and discounts are recorded at the time of sale to wholesale pharmaceutical distributors and pharmacies. We apply significant judgments and estimates in determining some of these allowances. If actual results differ from our estimates, we will be required to make adjustments to these allowances in the future. Our adjustments to gross sales are discussed further below.

Commercial Rebates

We participate in certain commercial rebate programs. Under these rebate programs, we pay a rebate to the commercial entity or third-party administrator of the program. We calculate accrued commercial rebate estimates using the expected value method. We accrue estimated rebates based on contract prices, estimated percentages of medicine that will be prescribed to qualified patients and estimated levels of inventory in the distribution channel and record the rebate as a reduction of revenue. Accrued commercial rebates are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Co-pay and Other Patient Assistance Programs

We offer discount card and other programs such as our HorizonCares program to patients under which the patient receives a discount on his or her prescription. In certain circumstances when a patient's prescription is rejected by a managed care vendor, we will pay for the full cost of the prescription. We reimburse pharmacies for this discount through third-party vendors. We reduce gross sales by the amount of actual co-pay and other patient assistance in the period based on invoices received. We also record an accrual to reduce gross sales for estimated co-pay and other patient assistance on units sold to distributors that have not yet been prescribed/dispensed to a patient. We calculate accrued co-pay and other patient assistance costs using the expected value method. The estimate is based on contract prices, estimated percentages of medicine that will be prescribed to qualified patients, average assistance paid based on reporting from the third-party vendors and estimated levels of inventory in the distribution channel. Accrued co-pay and other patient assistance costs are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Sales Returns

Consistent with industry practice, we maintain a return policy that allows customers to return certain medicines within a specified period prior to and subsequent to the medicine expiration date. Generally, medicines may be returned for a period beginning six months prior to its expiration date and up to one year after its expiration date. The right of return expires on the earlier of one year after the medicine expiration date or the time that the medicine is dispensed to the patient. The majority of medicine returns result from medicine dating, which falls within the range set by our policy, and are settled through the issuance of a credit to the customer. We calculate sales returns using the expected value method. The estimate of the provision for returns is based upon our historical experience with actual returns. The return period is known to us based on the shelf life of medicines at the time of shipment. We record sales returns in “accrued expenses and other current liabilities” and as a reduction of revenue.

Government Rebates

We participate in certain government rebate programs such as Medicare Coverage Gap and Medicaid. We calculate accrued government rebate estimates using the expected value method. A significant portion of these accruals relates to our Medicaid rebates. We accrue estimated rebates based on estimated percentages of medicine prescribed to qualified patients, estimated rebate percentages and estimated levels of inventory in the distribution channel that will be prescribed to qualified patients and record the rebates as a reduction of revenue. Accrued government rebates are included in “accrued trade discounts and rebates” on the consolidated balance sheet.

Chargebacks

We provide discounts to government qualified entities with whom we have contracted. These entities purchase medicines from the wholesale pharmaceutical distributors at a discounted price and the wholesale pharmaceutical distributors then charge back to us the difference between the current retail price and the contracted price that the entities paid for the medicines. We calculate accrued chargeback estimates using the expected value method. We accrue estimated chargebacks based on contract prices, sell-through sales data obtained from third-party information and estimated levels of inventory in the distribution channel and record the chargeback as a reduction of revenue. Accrued chargebacks are included in “accrued trade discounts and rebates” on the consolidated balance sheet.

Refer to Note 10, *Accrued Trade Discounts and Rebates*, of the Notes to our Consolidated Financial Statements included in Item 15 of this Annual Report on Form 10-K, which includes a table that summarizes changes in our customer-related accruals and allowances from December 31, 2019 to December 31, 2021.

Intangible Assets

Definite-lived intangible assets are amortized over their estimated useful lives. We review our intangible assets when events or circumstances may indicate that the carrying value of these assets is not recoverable and exceeds their fair value. We measure fair value based on the estimated future discounted cash flows associated with our assets in addition to other assumptions and projections that we deem to be reasonable and supportable. The estimated useful lives, from the date of acquisition, for all identified intangible assets that are subject to amortization are between five and thirteen years.

Indefinite-lived intangible assets consist of capitalized IPR&D. IPR&D assets represent capitalized incomplete research projects that we acquired through business combinations. Such assets are initially measured at their acquisition date fair values and are tested for impairment, until completion or abandonment of R&D efforts associated with the projects. An IPR&D asset is considered abandoned when R&D efforts associated with the asset have ceased, and there are no plans to sell or license the asset or derive value from the asset. At that point, the asset is considered to be impaired and is written off. Upon successful completion of each project, we will make a determination about the then remaining useful life of the intangible asset and begin amortization. We test indefinite-lived intangibles, including IPR&D assets, for impairment annually during the fourth quarter and more frequently if events or changes in circumstances indicate that it is more likely than not that the asset is impaired.

Business Combinations

We account for business combinations in accordance with the guidance in Accounting Standards Codification Topic 805, *Business Combinations*, under which acquired assets and liabilities are measured at their respective estimated fair values as of the acquisition date. We may be required, as in the case of intangible assets to determine the fair value associated with these amounts by estimating the fair value using an income approach under the discounted cash flow method, which may include revenue projections and other assumptions made by us to determine the fair value.

Goodwill

Goodwill represents the excess of the purchase price of acquired businesses over the estimated fair value of the identifiable net assets acquired. Goodwill is not amortized but is tested for impairment at least annually at the reporting unit level or more frequently if events or changes in circumstances indicate that the asset might be impaired. Impairment loss, if any, is recognized based on a comparison of the fair value of the asset to its carrying value, without consideration of any recoverability. We test goodwill for impairment annually during the fourth quarter and whenever indicators of impairment exist by first assessing qualitative factors to determine whether it is more likely than not that the fair value is less than its carrying amount. If we conclude it is more likely than not that the fair value of a reporting unit is less than its carrying amount, a quantitative impairment test is performed. If we conclude that goodwill is impaired, we will record an impairment charge in our consolidated statement of comprehensive income.

Provision for Income Taxes

We account for income taxes based upon an asset and liability approach. Deferred tax assets and liabilities represent the future tax consequences of the differences between the financial statement carrying amounts of assets and liabilities versus the tax basis of assets and liabilities. Under this method, deferred tax assets are recognized for deductible temporary differences, and operating loss and tax credit carryforwards. Deferred tax liabilities are recognized for taxable temporary differences. Deferred tax assets are reduced by a valuation allowance when, in the opinion of management, it is more likely than not that some portion or all of the deferred tax assets will not be realized. Significant judgment is required in determining whether it is probable that sufficient future taxable income will be available against which a deferred tax asset can be utilized. In determining future taxable income, we are required to make assumptions including the amount of taxable income in the various jurisdictions in which we operate. These assumptions require significant judgment about forecasts of future taxable income. Actual operating results in future years could render our current assumption of recoverability of deferred tax assets inaccurate. The impact of tax rate changes on deferred tax assets and liabilities is recognized in the period that the change is enacted. From time to time, we execute intercompany transactions in response to changes in operations, regulations, tax laws, funding needs and other circumstances. These transactions require the interpretation and application of tax laws in the applicable jurisdiction to support the tax treatment taken. The valuations which support the tax treatment of the transactions require significant estimates and assumptions within discounted cash flow models. We also account for the uncertainty in income taxes by utilizing a comprehensive model for the recognition, measurement, presentation and disclosure in financial statements of any uncertain tax positions that have been taken or are expected to be taken on an income tax return. Deferred tax assets and deferred tax liabilities are netted by each tax-paying entity within each jurisdiction in our consolidated balance sheets.

New Accounting Pronouncements Impacting Critical Accounting Policies

Refer to Note 2, *Summary of Significant Accounting Policies*, of the Notes to our Consolidated Financial Statements included in Item 15 of this Annual Report on Form 10-K, which includes a discussion of the new accounting pronouncements impacting critical accounting policies.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

We are exposed to various market risks, which include potential losses arising from adverse changes in market rates and prices, such as interest rates and foreign exchange fluctuations. We do not enter into derivatives or other financial instruments for trading or speculative purposes.

Interest Rate Risk. We are subject to interest rate fluctuation exposure through our borrowings under our Credit Agreement and our investment in money market accounts which bear a variable interest rate. Our approximately \$418.0 million aggregate principal amount of senior secured term loans borrowed under our Credit Agreement in December 2019, or the 2026 Term Loans, and loans under our incremental revolving credit facility, or Revolving Credit Facility, bear interest, at our option, at a rate equal to the London Inter-Bank Offered Rate, or LIBOR, plus 2.25% per annum (subject to a 0.00% LIBOR floor), or the adjusted base rate plus 1.25% per annum with a step-down to LIBOR plus 2.00% per annum or the adjusted base rate plus 1.00% per annum at the time our leverage ratio is less than or equal to 2.00 to 1.00. The adjusted base rate is defined as the greatest of (a) LIBOR (using one-month interest period) plus 1.00%, (b) the prime rate, (c) the federal funds rate plus 0.50%, and (d) 1.00%. Our 2026 Term Loans are borrowed in LIBOR. The one-month LIBOR rate as of February 24, 2022, which was the most recent date the interest rate on the 2026 Term Loans was fixed, was 0.19%, and as a result, the interest rate on our 2026 Term Loans is currently 2.19% per annum. Our \$1.6 billion aggregate principal amount of senior secured term loans borrowed under our Credit Agreement in March 2021, or the 2028 Term Loans, bear interest, at our option, at a rate equal to LIBOR, plus 2.00% per annum (subject to a 0.50% LIBOR floor), or the adjusted base rate plus 1.00% per annum with a step-down to LIBOR plus 1.75% per annum or the adjusted base rate plus 0.75% per annum at the time our leverage ratio is less than or equal to 2.00 to 1.00. Our 2028 Term Loans are based on LIBOR. The one-month LIBOR rate as of February 24, 2022, which was the most recent date the interest rate on the 2028 Term Loans was fixed, was 0.13%, and as a result, the interest rate on our 2028 Term Loans is currently 2.25% per annum. As of December 31, 2021, the Revolving Credit Facility was undrawn. Because the United Kingdom Financial Conduct Authority, which regulates LIBOR, intended to phase out the use of LIBOR by the end of 2021, future borrowings under our Credit Agreement could be subject to reference rates other than LIBOR. However, the cessation date has been deferred to June 30, 2023 for the most commonly used tenors in U.S. dollar LIBOR (i.e., overnight and one, three and six months). We do not expect the planned discontinuation of LIBOR to have a material impact on interest payments incurred under our Credit Agreement.

An increase in the LIBOR of 100 basis points above the current rate would increase our interest expense related to the Credit Agreement by \$14.1 million per year.

The goals of our investment policy are to preserve capital, fulfill liquidity needs and maintain fiduciary control of cash. To achieve our goal of maximizing income without assuming significant market risk, we maintain our excess cash and cash equivalents in money market funds, time deposits and U.S. federal government securities. Because of the short-term maturities of our cash equivalents, we do not believe that a decrease in interest rates would have any material negative impact on the fair value of our cash equivalents.

Foreign Currency Risk. Our purchase costs of TEPEZZA drug substance, TEPEZZA drug product with our recently approved second drug product manufacturer, Patheon Pharmaceuticals Inc. (contract development and manufacturing organization services of Thermo Fisher Scientific), and ACTIMMUNE inventory are principally denominated in Euros and are subject to foreign currency risk. In addition, we are obligated to pay certain milestones and a royalty on sales of TEPEZZA to Roche in Swiss Francs, which obligations are subject to foreign currency risk. We have contracts relating to RAVICTI, QUINSAIR and PROCYSBI for sales in Canada which sales are subject to foreign currency risk. We also incur certain operating expenses in currencies other than the U.S. dollar in relation to our Irish operations and foreign subsidiaries. Therefore, we are subject to volatility in cash flows due to fluctuations in foreign currency exchange rates, particularly changes in the Euro and the Swiss Franc. From time to time, we may enter into forward currency contracts to hedge our foreign currency risk exposure.

Inflation Risk. We do not believe that inflation has had a material impact on our business or results of operations during the periods for which the financial statements are presented in this report.

Credit Risk. Historically, our accounts receivable balances have been highly concentrated with a select number of customers, consisting primarily of large wholesale pharmaceutical distributors who, in turn, sell the medicines to pharmacies, hospitals and other customers. As of December 31, 2021 and 2020, our top four customers accounted for approximately 94% and 93%, respectively, of our total outstanding accounts receivable balances. Given the size and creditworthiness of the customers, we have not experienced and do not expect to experience material credit related losses with such customers.

Item 8. Financial Statements and Supplementary Data

The financial information required by Item 8 is contained in Part IV, Item 15 of this Annual Report on Form 10-K.

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

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our Chief Executive Officer and Chief Financial Officer, after evaluating the effectiveness of our “disclosure controls and procedures” (as defined in Rule 13a-15(e) promulgated under the Securities Exchange Act of 1934, as amended, or the Exchange Act), have concluded that, as of December 31, 2021, our disclosure controls and procedures were effective to provide reasonable assurance that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the Securities and Exchange Commission’s rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by an issuer in the reports that it files or submits under the Exchange Act is accumulated and communicated to the issuer’s management, including its principal executive officer or officers and principal financial officer or officers, or persons performing similar functions, as appropriate to allow timely decisions regarding required disclosure.

Management’s Report on Internal Control over Financial Reporting

Our management, under the supervision of our Chief Executive Officer and our Chief Financial Officer, is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined under Rule 13a-15(f) of the Exchange Act. Internal control over financial reporting is designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation.

Our management has assessed the effectiveness of our internal control over financial reporting as of December 31, 2021. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in *Internal Control – Integrated Framework (2013)*. Management’s assessment included an evaluation of the design of our internal control over financial reporting and testing of the operational effectiveness of our internal control over financial reporting. Based on management’s assessment, management has concluded that, as of December 31, 2021, our internal control over financial reporting was effective based on those criteria.

The effectiveness of our internal control over financial reporting as of December 31, 2021, has been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm, as stated in their report which appears herein.

Changes in Internal Control Over Financial Reporting

There have been no material changes to our internal control over financial reporting, as defined in Exchange Act Rules 13a-15(f) and 15d-15(f), during the three months ended December 31, 2021, that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None

Item 9C. 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 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:

- 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 delinquent Section 16(a) reports, if any, is to be included in the section entitled “Delinquent Section 16(a) Reports;” and
- 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 “The Board of Directors and its Committees.”

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.

We have adopted a written Code of Conduct and Ethics, or Ethics Code, that applies to all officers, directors and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. The Ethics Code is available on our website at www.horizontherapeutics.com. If we make any substantive amendments to the Ethics Code or grant any waiver from a provision of the Ethics Code to any executive officer or director, we will promptly disclose the nature of the amendment or waiver on our website or in a Current Report on Form 8-K.

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,” “Non-Employee Director Compensation,” “The Board of Directors and its Committees—Compensation Committee Interlocks and Insider Participation” and “Compensation Discussion and Analysis” and is incorporated herein by reference, 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.

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 “Other Information—Security Ownership of Certain Beneficial Owners and Management” and in each case is incorporated herein by reference, 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.

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 Transactions” and “The Board of Directors and its Committees—Independence of the Board of Directors” and is incorporated herein by reference, 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.

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—Approve Appointment of Independent Registered Public Accounting Firm and Authorized the Audit Committee to Determine the Auditors’ Remuneration” and is incorporated herein by reference, 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.

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a) Documents filed as part of this report.

1. Financial Statements

The financial statements listed on the Index to Consolidated Financial Statements F-1 to F-59 are filed as part of this Annual Report on Form 10-K.

2. Financial Statement Schedules

Schedule II – Valuation and Qualifying Accounts and Reserves for each of the three fiscal years ended December 31, 2021, 2020 and 2019 appearing on page F-59. Other financial statement schedules have been omitted because the required information is included in the consolidated financial statements or notes thereto or because they are not applicable or not required.

3. Exhibits

INDEX TO EXHIBITS

<u>Exhibit Number</u>	<u>Description of Document</u>
2.1#	Agreement and Plan of Merger, dated January 31, 2021, by and among Horizon Therapeutics USA, Inc., Teiripic Merger Sub, Inc., Viela Bio, Inc. and solely for purposes of Sections 6.7 and 9.12 of the Merger Agreement, Horizon Therapeutics plc (incorporated by reference to Exhibit 2.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on February 1, 2021).
3.1	Memorandum and Articles of Association of Horizon Therapeutics Public Limited Company, as amended (incorporated by reference to Exhibit 3.1 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on May 8, 2019).
4.1	Indenture dated as of July 16, 2019 by and between Horizon Therapeutics USA, Inc., the guarantors party thereto and U.S. Bank National Association, as trustee (incorporated by reference to Exhibit 4.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on July 16, 2019).
4.2	Form of 5.500% Senior Note due 2027 (incorporated by reference to Exhibit 4.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on July 16, 2019).
4.3	First Supplemental Indenture, dated November 19, 2019, by and between HZNP Finance Limited and U.S. Bank National Association (incorporated by reference to Exhibit 4.5 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on May 6, 2020).
4.4	Second Supplemental Indenture, dated April 23, 2020, by and among Horizon Properties Holding LLC, Curzion Pharmaceuticals, Inc. and U.S. Bank National Association (incorporated by reference to Exhibit 4.6 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on May 6, 2020).
4.5	Third Supplemental Indenture, dated March 15, 2021, by and between Viela Bio, Inc. and U.S. Bank National Association (incorporated by reference to Exhibit 4.5 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on May 5, 2021).
4.6	Description of securities registered under Section 12 of the Exchange Act of 1934 (incorporated by reference to Exhibit 4.6 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 26, 2020).
10.1+	Form of Indemnification Agreement entered into by and between Horizon Therapeutics Public Limited Company and certain of its directors, officers and employees (incorporated by reference to Exhibit 10.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on September 19, 2014).
10.2+	Form of Indemnification Agreement entered into by and between Horizon Therapeutics USA, Inc. and certain directors, officers and employees of Horizon Therapeutics Public Limited Company (incorporated by reference to Exhibit 10.2 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on September 19, 2014).
10.3+	Horizon Therapeutics Public Limited Company Non-Employee Director Compensation Policy, as amended.
10.4+	Horizon Therapeutics USA, Inc. 2011 Equity Incentive Plan, as amended, and Form of Option Agreement and Form of Stock Option Grant Notice thereunder (incorporated by reference to Exhibit 99.1 to Horizon Therapeutics, Inc.'s Current Report on Form 8-K, filed on July 2, 2014).
10.5+	Horizon Therapeutics Public Limited Company Amended and Restated 2014 Equity Incentive Plan and Form of Option Agreement, Form of Stock Option Grant Notice, Forms of Restricted Stock Unit Agreement and Forms of Restricted Stock Unit Grant Notice thereunder (incorporated by reference to Exhibit 10.7 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on May 8, 2019).

- 10.6⁺ Horizon Therapeutics Public Limited Company 2014 Non-Employee Equity Plan, as amended, and Form of Option Agreement, Form of Stock Option Grant Notice, Forms of Restricted Stock Unit Agreement and Forms of Restricted Stock Unit Grant Notice thereunder (incorporated by reference to Exhibit 10.3 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on November 3, 2021).
- 10.7⁺ Form of Employee Proprietary Information and Inventions Agreement (incorporated by reference to Exhibit 10.15 to Horizon Pharma, Inc.'s Registration Statement on Form S-1 (No. 333-168504), as amended).
- 10.8⁺ Amended and Restated Executive Employment Agreement, dated July 27, 2010, by and between Horizon Therapeutics USA, Inc. and Timothy P. Walbert (incorporated by reference to Exhibit 10.22 to Horizon Pharma, Inc.'s Registration Statement on Form S-1 (No. 333-168504), as amended).
- 10.9⁺ First Amendment to Amended and Restated Executive Employment Agreement, dated January 16, 2014, by and between Horizon Therapeutics USA, Inc. and Timothy P. Walbert (incorporated by reference to Exhibit 99.1 to Horizon Pharma, Inc.'s Current Report on Form 8-K, filed on January 16, 2014).
- 10.10⁺ Executive Employment Agreement, effective as of June 23, 2014, by and between Horizon Therapeutics USA, Inc. and Paul W. Hoelscher (incorporated by reference to Exhibit 99.4 to Horizon Pharma, Inc.'s Current Report on Form 8-K, filed on June 18, 2014).
- 10.11⁺ Horizon Therapeutics USA, Inc. Deferred Compensation Plan (incorporated by reference to Exhibit 10.30 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 28, 2018).
- 10.12⁺ Horizon Therapeutics Public Limited Company Equity Long-Term Incentive Program (incorporated by reference to Exhibit 10.2 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on May 8, 2015).
- 10.13 Credit Agreement, dated May 7, 2015, by and among Horizon Therapeutics USA, Inc., as borrower, Horizon Therapeutics Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 10.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on May 11, 2015).
- 10.14* License Agreement, dated April 16, 1999, by and among Saul Brusilow, M.D., Brusilow Enterprises, Inc. and Horizon Therapeutics, LLC (as successor in interest to Medicis Pharmaceutical Corporation) (incorporated by reference to Exhibit 10.17 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 24, 2021).
- 10.15* Settlement Agreement and First Amendment to License Agreement, dated August 21, 2007, by and among Saul Brusilow, M.D., Brusilow Enterprises, Inc., and Horizon Therapeutics, LLC (as successor in interest to Medicis Pharmaceutical Corporation and Ucylyd Pharma, Inc.) (incorporated by reference to Exhibit 10.18 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 24, 2021).
- 10.16⁺ Horizon Therapeutics Public Limited Company Share Clog Program Trust Deed, as amended, and Form of Clog Letter (incorporated by reference to Exhibit 10.6 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on August 8, 2016).
- 10.17* License Agreement, dated August 12, 1998, by and among Mountain View Pharmaceuticals, Inc., Duke University and Horizon Therapeutics Ireland DAC (as successor in interest to Bio-Technology General Corporation), as amended November 12, 2001, August 30, 2010, March 12, 2014 and July 16, 2015 (incorporated by reference to Exhibit 10.20 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 24, 2021).

- 10.18* Commercial Supply Agreement, dated March 20, 2007, by and between Horizon Therapeutics Ireland DAC (as successor in interest to Savient Pharmaceuticals, Inc.) and Bio-Technology General (Israel) Ltd., as amended September 24, 2007, January 24, 2009, July 1, 2010 and March 21, 2012 (incorporated by reference to Exhibit 10.21 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 24, 2021).
- 10.19* Supply Agreement, dated August 3, 2015, by and between NOF Corporation and Horizon Therapeutics Ireland DAC (as successor in interest to Crealta Pharmaceuticals LLC) (incorporated by reference to Exhibit 10.22 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 24, 2021).
- 10.20* Asset Purchase Agreement, dated March 22, 2012, by and between Horizon Therapeutics, LLC (as successor in interest to Hyperion Therapeutics, Inc.) and Bausch Health Companies Inc. (formerly Ucyclyd Pharma, Inc.) (incorporated by reference to Exhibit 10.23 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 24, 2021).
- 10.21* Commercial Supply Agreement, dated October 16, 2008, by and between Exelead, Inc. (formerly known as Sigma-Tau PharmaSource, Inc. (as successor in interest to Enzon Pharmaceuticals, Inc.)) and Horizon Therapeutics Ireland DAC (as successor in interest to Savient Pharmaceuticals, Inc.), as amended October 5, 2009, October 22, 2009 and July 29, 2014 (incorporated by reference to Exhibit 10.24 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 24, 2021).
- 10.22* Fifth Amendment to Commercial Supply Agreement, effective as of August 31, 2016, by and between Horizon Therapeutics Ireland DAC and Bio-Technology General (Israel) Ltd (incorporated by reference to Exhibit 10.25 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 24, 2021).
- 10.23 Amendment No. 1, dated October 25, 2016, to Credit Agreement, dated May 7, 2015, by and among Horizon Therapeutics USA, Inc., as borrower, Horizon Therapeutics Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on October 25, 2016).
- 10.24* API Supply Agreement, dated November 3, 2010, by and between Cambrex Profarmaco Milano and Horizon Therapeutics Ireland DAC (as successor in interest to Raptor Therapeutics Inc. and Raptor Pharmaceuticals Europe B.V.), as amended April 9, 2013 (incorporated by reference to Exhibit 10.4 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on November 2, 2020).
- 10.25* Manufacturing Services Agreement, dated November 15, 2010, by and among Patheon Pharmaceuticals Inc., Horizon Orphan LLC (as successor in interest to Raptor Therapeutics Inc.) and Horizon Pharma Europe B.V. (as successor in interest to Raptor Pharmaceuticals Europe B.V.), as amended April 5, 2012 and June 21, 2013 (incorporated by reference to Exhibit 10.28 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 24, 2021).
- 10.26+ Horizon Therapeutics Public Limited Company Equity Long-Term Incentive Program (incorporated by reference to Exhibit 99.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on January 11, 2018).
- 10.27+ Horizon Therapeutics Public Limited Company Cash Incentive Program (incorporated by reference to Exhibit 99.2 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on January 11, 2018).
- 10.28+ Horizon Therapeutics Public Limited Company Incentive Compensation Recoupment Policy (incorporated by reference to Exhibit 99.4 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on January 11, 2018).

- 10.29 Amendment No. 2, dated March 29, 2017, to Credit Agreement, dated May 7, 2015, as amended, by and among Horizon Therapeutics USA, Inc., as Borrower, Horizon Therapeutics Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on March 30, 2017).
- 10.30 Amendment No. 3, dated October 23, 2017, to Credit Agreement, dated May 7, 2015, as amended, by and among Horizon Therapeutics USA, Inc., as Borrower, Horizon Therapeutics Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on October 23, 2017).
- 10.31* Amended and Restated License Agreement, dated May 31, 2017, by and between Horizon Orphan LLC and The Regents of the University of California (incorporated by reference to Exhibit 10.35 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 24, 2021).
- 10.32+ First Amendment to Executive Employment Agreement, dated May 4, 2017, by and between Horizon Therapeutics USA, Inc. and Paul W. Hoelscher (incorporated by reference to Exhibit 10.7 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2017).
- 10.33+ Second Amendment to Amended and Restated Executive Employment Agreement, dated May 4, 2017, by and between Horizon Therapeutics USA, Inc. and Timothy P. Walbert (incorporated by reference to Exhibit 10.13 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2017).
- 10.34+ Executive Employment Agreement, effective as of February 16, 2017, by and between Horizon Therapeutics USA, Inc. and Michael DesJardin (incorporated by reference to Exhibit 10.68 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 28, 2018).
- 10.35+ First Amendment to Executive Employment Agreement, dated May 4, 2017, by and between Horizon Therapeutics USA, Inc. and Michael DesJardin (incorporated by reference to Exhibit 10.69 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 28, 2018).
- 10.36** Confidential Settlement and License Agreement, effective as of June 27, 2018, by and among Horizon Therapeutics, LLC, Lupin Ltd. and Lupin Pharmaceuticals, Inc. (incorporated by reference to Exhibit 10.1 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on August 8, 2018).
- 10.37** Confidential Settlement and License Agreement, effective as of September 17, 2018, by and between Horizon Therapeutics, LLC and Par Pharmaceutical, Inc. (incorporated by reference to Exhibit 10.1 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on November 7, 2018).
- 10.38 Amendment No. 4, dated October 19, 2018, to Credit Agreement, dated May 7, 2015, as amended, by and among Horizon Therapeutics USA, Inc., as Borrower, Horizon Therapeutics Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on October 19, 2018).
- 10.39** Amendment No. 1 to Amended and Restated License Agreement, dated September 11, 2018, by and between Horizon Orphan LLC and The Regents of the University of California (incorporated by reference to Exhibit 10.3 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on November 7, 2018).

- 10.40 Amendment No. 5, dated March 11, 2019, to Credit Agreement, dated May 7, 2015, as amended, by and among Horizon Therapeutics USA, Inc., as Borrower, Horizon Therapeutics Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on March 11, 2019).
- 10.41* Commercial Supply Agreement, effective as of February 14, 2018, by and between CMC Biologics A/S, dba AGC Biologics and Horizon Therapeutics Ireland DAC (incorporated by reference to Exhibit 10.3 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on May 8, 2019).
- 10.42* Commercial Supply Agreement, effective as of December 18, 2018, by and between Catalent Indiana, LLC and Horizon Therapeutics Ireland DAC (incorporated by reference to Exhibit 10.4 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on May 8, 2019).
- 10.43* License Agreement, effective as of June 15, 2011, by and among F. Hoffmann-La Roche Ltd, Hoffman-La Roche Inc. and Horizon Therapeutics Ireland DAC (as successor in interest to River Vision Development Corp), as amended through Amendment No. 9 to the License Agreement, effective as of October 21, 2016 (incorporated by reference to Exhibit 10.70 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 26, 2020).
- 10.44 Amendment No. 6, dated May 22, 2019, to Credit Agreement, dated May 7, 2015, as amended, by and among Horizon Therapeutics USA, Inc., as Borrower, Horizon Therapeutics Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on May 22, 2019).
- 10.45* Amendment No. 1 to Commercial Supply Agreement, dated May 15, 2019, by and between AGC Biologics A/S (formerly known as CMC Biologics A/S) and Horizon Therapeutics Ireland DAC (incorporated by reference to Exhibit 10.6 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on August 7, 2019).
- 10.46* Mutual Settlement, Release and Media License Agreement, effective as of December 21, 2016, by and between Horizon Therapeutics Ireland DAC (as successor in interest to River Vision Development Corp) and Boehringer Ingelheim Biopharmaceuticals GmbH (incorporated by reference to Exhibit 10.1 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on November 6, 2019).
- 10.47+ Executive Employment Agreement, effective as of November 1, 2019, by and among Horizon Therapeutics Public Limited Company, Horizon Therapeutics USA, Inc. and Andy Pasternak (incorporated by reference to Exhibit 10.3 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on November 6, 2019).
- 10.48 Amendment No. 7, dated December 18, 2019, to Credit Agreement, dated May 7, 2015, as amended, by and among Horizon Therapeutics USA, Inc., as Borrower, Horizon Therapeutics Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on December 18, 2019).
- 10.49* Amendment No. 2 to Commercial Supply Agreement, dated December 18, 2019, by and between AGC Biologics A/S (formerly known as CMC Biologics A/S) and Horizon Therapeutics Ireland DAC (incorporated by reference to Exhibit 10.78 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 26, 2020).
- 10.50 Amendment No. 2 to API Supply Agreement, effective as of January 17, 2018, by and between Cambrex Profarmaco Milano and Horizon Therapeutics Ireland DAC (incorporated by reference to Exhibit 10.79 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 26, 2020).

- 10.51* Amendment to Supply Agreement, effective as of November 30, 2018, by and between NOF Corporation and Horizon Therapeutics Ireland DAC (incorporated by reference to Exhibit 10.80 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 26, 2020).
- 10.52+ Horizon Therapeutics Public Limited Company Amended and Restated 2020 Equity Incentive Plan, as amended, and 2020 Restricted Stock Unit Award Sub-Plan and Form of Option Agreement, Form of Stock Option Grant Notice, Forms of Restricted Stock Unit Agreement and Forms of Restricted Stock Unit Grant Notice thereunder.
- 10.53+ Horizon Therapeutics Public Limited Company 2020 Employee Share Purchase Plan (incorporated by reference to Exhibit 99.2 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on May 1, 2020).
- 10.54* Amendment No. 3 to Commercial Supply Agreement, dated July 30, 2020, by and between AGC Biologics A/S (formerly known as CMC Biologics A/S) and Horizon Therapeutics Ireland DAC (incorporated by reference to Exhibit 10.1 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on November 2, 2020).
- 10.55* Development and Manufacturing Services Agreement, dated June 10, 2015, by and between AGC Biologics A/S (formerly known as CMC Biologics A/S) and Horizon Therapeutics Ireland DAC (as successor in interest to River Vision Development Corp) (incorporated by reference to Exhibit 10.2 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on November 2, 2020).
- 10.56 Incremental Amendment and Lender Joinder Agreement, dated August 17, 2020, by and among JP Morgan Chase Bank, N.A., as an incremental revolving lender and as an issuing bank, Horizon Therapeutics USA, Inc. and Citibank, N.A., as administrative agent (incorporated by reference to Exhibit 10.3 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on November 2, 2020).
- 10.57+ Amended and Restated Executive Employment Agreement, effective as of July 27, 2010, as amended, by and between Horizon Therapeutics USA, Inc. and Jeffrey W. Sherman, M.D. (incorporated by reference to Exhibit 10.69 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 24, 2021).
- 10.58* Second Amendment to Supply Agreement, effective as of January 22, 2021, by and between NOF Corporation and Horizon Therapeutics Ireland DAC (incorporated by reference to Exhibit 10.70 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 24, 2021).
- 10.59 Assignment and Amendment of Development and Manufacturing Services Agreement, dated February 14, 2018, by and between AGC Biologics A/S (formerly known as CMC Biologics A/S) and Horizon Therapeutics Ireland DAC (as successor in interest to River Vision Development Corp) (incorporated by reference to Exhibit 10.72 to Horizon Therapeutics Public Limited Company's Annual Report on Form 10-K, filed on February 24, 2021).
- 10.60 Amendment No. 9, dated March 15, 2021, to the Credit Agreement, dated May 7, 2015, as amended, by and among Horizon Therapeutics USA, Inc., as Borrower, Horizon Therapeutics Public Limited Company, as Irish Holdco and a guarantor, the subsidiary guarantors party thereto, as subsidiary guarantors, the lenders party thereto and Citibank, N.A., as administrative agent and collateral agent (incorporated by reference to Exhibit 99.1 to Horizon Therapeutics Public Limited Company's Current Report on Form 8-K, filed on March 15, 2021).
- 10.61+ Executive Employment Agreement, effective as of March 15, 2021, by and among Horizon Therapeutics Public Limited Company, Horizon Therapeutics USA, Inc. and Elizabeth H.Z. Thompson (incorporated by reference to Exhibit 10.5 to Horizon Therapeutics Public Limited Company's Quarterly Report on Form 10-Q, filed on May 5, 2021).
- 10.62+ Horizon Therapeutics Public Limited Company Amended and Restated 2018 Equity Incentive Plan (assumed from Viela Bio, Inc.), as amended, and 2018 Restricted Stock Unit Award Sub-Plan and Forms of RSU Award Grant Notice and Forms of Award Agreement (RSU Award) thereunder.

10.63*	Master Manufacturing Services Agreement, dated October 15, 2018, by and between Patheon Pharmaceuticals Inc. and Horizon Medicines LLC.
10.64+	Release and Waiver of Claims of Brian Beeler, dated as of January 6, 2022.
10.65+	Release and Waiver of Claims of Barry Moze, dated as of January 10, 2022.
10.66+	Executive Employment Agreement, effective as of February 28, 2022, by and among Horizon Therapeutics Public Limited Company, Horizon Therapeutics USA, Inc. and Sean M. Clayton.
21.1	Subsidiaries of Horizon Therapeutics Public Limited Company.
23.1	Consent of PricewaterhouseCoopers LLP, independent registered public accounting firm.
24.1	Power of Attorney. Reference is made to the signature page hereto.
31.1	Certification of Principal Executive Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Exchange Act.
31.2	Certification of Principal Financial Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Exchange Act.
32.1	Certification of Principal Executive Officer pursuant to Rule 13a-14(b) or 15d-14(b) of the Exchange Act and 18 U.S.C. Section 1350.
32.2	Certification of Principal Financial Officer pursuant to Rule 13a-14(b) or 15d-14(b) of the Exchange Act and 18 U.S.C. Section 1350.
101.INS	Inline XBRL Instance Document – the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document
101.SCH	Inline XBRL Taxonomy Extension Schema Document
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101)

Schedules have been omitted pursuant to Item 601(a)(5) of Regulation S-K. The registrant hereby undertakes to furnish supplemental copies of any of the omitted schedules upon request by the U.S. Securities and Exchange Commission.

+ Indicates management contract or compensatory plan.

* Certain information in this exhibit has been omitted pursuant to Item 601 of Regulation S-K.

** Confidential treatment has been granted with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

Item 16. Form 10-K Summary

None.

HORIZON THERAPEUTICS PLC
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Report of Independent Registered Public Accounting Firm

To the Board of Directors and Shareholders of Horizon Therapeutics plc

Opinions on the Financial Statements and Internal Control over Financial Reporting

We have audited the accompanying consolidated balance sheets of Horizon Therapeutics plc and its subsidiaries (the “Company”) as of December 31, 2021 and 2020, and the related consolidated statements of comprehensive income, of shareholders' equity and of cash flows for each of the three years in the period ended December 31, 2021, including the related notes and financial statement schedule listed in the index appearing under Item 15(a)(2) (collectively referred to as the “consolidated financial statements”). We also have audited the Company's internal control over financial reporting as of December 31, 2021, based on criteria established in *Internal Control - Integrated Framework* (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO).

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of the Company as of December 31, 2021 and 2020, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2021 in conformity with accounting principles generally accepted in the United States of America. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2021, based on criteria established in *Internal Control - Integrated Framework* (2013) issued by the COSO.

Change in Accounting Principle

As discussed in Note 2 to the consolidated financial statements, the Company changed the manner in which it accounts for leases in 2019.

Basis for Opinions

The Company's management is responsible for these consolidated financial statements, for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting, included in Management’s Report on Internal Control over Financial Reporting appearing under Item 9A. Our responsibility is to express opinions on the Company’s consolidated financial statements and on the Company's internal control over financial reporting based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud, and whether effective internal control over financial reporting was maintained in all material respects.

Our audits of the consolidated financial statements included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide a reasonable basis for our opinions.

Definition and Limitations of Internal Control over Financial Reporting

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

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

Critical Audit Matters

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

Accrued Medicaid Rebates

As described in Notes 2 and 10 to the consolidated financial statements, the Company has accrued government rebates and chargebacks of \$222.6 million as of December 31, 2021. A significant portion of these accruals relates to the Company's Medicaid rebates. Management calculates the Medicaid rebate allowance using the expected value method. Management accrues estimated rebates based on estimated percentages of medicine prescribed to qualified patients, estimated rebate percentages and estimated levels of inventory in the distribution channel that will be prescribed to qualified patients and records the rebates as a reduction of revenue.

The principal considerations for our determination that performing procedures relating to accrued Medicaid rebates is a critical audit matter are (i) the significant judgment by management when determining the allowance, and (ii) the high degree of auditor judgment, subjectivity and effort in performing procedures and evaluating audit evidence related to management's estimate and significant assumptions related to estimated percentages of medicine prescribed to qualified patients, estimated rebate percentages and estimated levels of inventory in the distribution channel that will be prescribed to qualified patients.

Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming our overall opinion on the consolidated financial statements. These procedures included testing the effectiveness of controls relating to accrued Medicaid rebates, including controls over the assumptions used to estimate the allowance. These procedures also included, among others, (i) developing an independent estimate of the accrued Medicaid rebates by utilizing third-party prescription data, the terms of the specific rebate programs, and the historical trend of actual rebate claims paid, (ii) comparing the independent estimate to management's estimate to evaluate the reasonableness of the estimate, (iii) testing rebate claims processed by the Company, including evaluating those claims for consistency with the terms of the specific rebate programs, (iv) testing the completeness, accuracy and relevance of the underlying data used by management, and (v) evaluating the significant assumptions used by management related to estimated percentages of medicine prescribed to qualified patients, estimated rebate percentages and estimated levels of inventory in the distribution channel that will be prescribed to qualified patients. Evaluating management's assumptions involved evaluating whether the assumptions were reasonable considering (i) the consistency of the assumptions with historical trends, (ii) comparing assumptions and inputs to government prices, invoices, current payment trends, and other third-party data on a test basis where relevant, (iii) whether relevant company and industry specific considerations have been incorporated into the assumptions, and (iv) whether these assumptions were consistent with evidence obtained in other areas of the audit.

Valuation of Developed Technology Asset - Acquisition of Viela Bio, Inc.

As described in Notes 1 and 4 to the consolidated financial statements, on March 15, 2021, the Company completed its acquisition of Viela Bio, Inc. (“Viela”) and acquired all of the issued and outstanding shares of Viela’s common stock for approximately \$3.0 billion. Identifiable assets and liabilities of Viela, including identifiable intangible assets, were recorded based on their estimated fair values as of the date of the closing of the acquisition, which included a developed technology intangible asset of \$1.5 billion. The fair value of developed technology was determined using an income approach. Some of the most significant assumptions inherent in the development of the asset valuation include the estimated net cash flows for each year (including net sales, cost of goods sold, sales and marketing costs, and R&D costs) and the discount rate.

The principal considerations for our determination that performing procedures relating to the valuation of the developed technology asset from the Viela acquisition is a critical audit matter are (i) the significant judgment by management when determining the fair value of the developed technology asset acquired, (ii) the high degree of auditor judgment, subjectivity, and effort in performing procedures and evaluating management’s significant assumptions related to net sales, cost of goods sold, sales and marketing costs, and discount rate, and (iii) the audit effort involved the use of professionals with specialized skill and knowledge.

Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming our overall opinion on the consolidated financial statements. These procedures included testing the effectiveness of controls relating to the acquisition accounting, including controls over management’s valuation of the developed technology asset and controls over the development of significant assumptions related to net sales, cost of goods sold, sales and marketing costs, and discount rate. These procedures also included, among others (i) reading the purchase agreement, (ii) testing management’s process for determining the fair value of the developed technology asset, (iii) evaluating the appropriateness of the income valuation approach, (iv) testing the completeness, accuracy and relevance of the underlying data used by management in the approach, and (iv) evaluating the reasonableness of the significant assumptions used by management related to net sales, cost of goods sold, sales and marketing costs, and discount rate. Evaluating management’s significant assumptions related to net sales, cost of goods sold, and sales and marketing costs involved evaluating whether the significant assumptions used by management were reasonable considering (i) the current and past performance of Viela, (ii) the consistency with external market and industry data, and (iii) whether these assumptions were consistent with evidence obtained in other areas of the audit. Professionals with specialized skill and knowledge were used to assist in evaluating (i) the appropriateness of the income valuation approach and (ii) the reasonableness of the discount rate significant assumption.

/s/ PricewaterhouseCoopers LLP
Chicago, Illinois
March 1, 2022

We have served as the Company’s auditor since 2009.

HORIZON THERAPEUTICS PLC
CONSOLIDATED BALANCE SHEETS
(In thousands, except nominal value and share data)

	As of December 31, 2021	As of December 31, 2020
ASSETS		
CURRENT ASSETS:		
Cash and cash equivalents	\$ 1,580,317	\$ 2,079,906
Restricted cash	3,839	3,573
Accounts receivable, net	632,775	659,701
Inventories, net	225,730	75,283
Prepaid expenses and other current assets	357,106	251,945
Total current assets	2,799,767	3,070,408
Property, plant and equipment, net	292,298	189,037
Developed technology and other intangible assets, net	2,960,118	1,782,962
In-process research and development	880,000	—
Goodwill	1,066,709	413,669
Deferred tax assets, net	538,098	560,841
Other assets	140,738	55,699
Total assets	\$ 8,677,728	\$ 6,072,616
LIABILITIES AND SHAREHOLDERS' EQUITY		
CURRENT LIABILITIES:		
Accounts payable	\$ 30,125	\$ 37,710
Accrued expenses and other current liabilities	523,015	485,567
Accrued trade discounts and rebates	317,431	352,463
Long-term debt—current portion	16,000	—
Total current liabilities	886,571	875,740
LONG-TERM LIABILITIES:		
Long-term debt, net	2,555,233	1,003,379
Deferred tax liabilities, net	390,455	66,474
Other long-term liabilities	173,076	101,672
Total long-term liabilities	3,118,764	1,171,525
COMMITMENTS AND CONTINGENCIES		
SHAREHOLDERS' EQUITY:		
Ordinary shares, \$0.0001 nominal value; 600,000,000 shares authorized at December 31, 2021 and December 31, 2020; 227,760,936 and 221,721,674 shares issued at December 31, 2021 and December 31, 2020, respectively; and 227,376,570 and 221,337,308 shares outstanding at December 31, 2021 and December 31, 2020, respectively	23	22
Treasury stock, 384,366 ordinary shares at December 31, 2021 and December 31, 2020	(4,585)	(4,585)
Additional paid-in capital	4,373,337	4,245,945
Accumulated other comprehensive loss	(14,987)	(145)
Retained earnings (accumulated deficit)	318,605	(215,886)
Total shareholders' equity	4,672,393	4,025,351
Total liabilities and shareholders' equity	\$ 8,677,728	\$ 6,072,616

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

HORIZON THERAPEUTICS PLC
CONSOLIDATED STATEMENTS OF COMPREHENSIVE INCOME
(In thousands, except share and per share data)

	For the Years Ended December 31,		
	2021	2020	2019
Net sales	\$ 3,226,410	\$ 2,200,429	\$ 1,300,029
Cost of goods sold	794,512	532,695	362,175
Gross profit	2,431,898	1,667,734	937,854
OPERATING EXPENSES:			
Research and development	431,990	209,364	103,169
Selling, general and administrative	1,446,410	973,227	697,111
Impairment of long-lived asset	12,371	—	—
(Gain) loss on sale of assets	(2,000)	(4,883)	10,963
Total operating expenses	1,888,771	1,177,708	811,243
Operating income	543,127	490,026	126,611
OTHER EXPENSE, NET:			
Interest expense, net	(81,063)	(59,616)	(87,089)
Foreign exchange (loss) gain	(1,028)	(297)	33
Loss on debt extinguishment	—	(31,856)	(58,835)
Other income (expense), net	1,791	3,388	(944)
Total other expense, net	(80,300)	(88,381)	(146,835)
Income (loss) before (benefit) expense for income taxes	462,827	401,645	(20,224)
(Benefit) expense for income taxes	(71,664)	11,849	(593,244)
Net income	\$ 534,491	\$ 389,796	\$ 573,020
Net income per ordinary share—basic	\$ 2.37	\$ 1.91	\$ 3.13
Weighted average ordinary shares outstanding—basic	225,551,410	203,967,246	182,930,109
Net income per ordinary share—diluted	\$ 2.27	\$ 1.81	\$ 2.90
Weighted average ordinary shares outstanding—diluted	235,680,483	215,308,768	205,224,221
OTHER COMPREHENSIVE (LOSS) INCOME, NET OF TAX			
Pension and other post-employment benefit plan remeasurements	\$ (13,296)	\$ —	\$ —
Foreign currency translation adjustments	(1,546)	1,760	(382)
Other comprehensive (loss) income	(14,842)	1,760	(382)
Comprehensive income	\$ 519,649	\$ 391,556	\$ 572,638

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

HORIZON THERAPEUTICS PLC
CONSOLIDATED STATEMENTS OF SHAREHOLDERS' EQUITY
(In thousands, except share data)

	Ordinary Shares		Treasury Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Retained Earnings (Accumulated Deficit)	Total Shareholders' Equity
	Shares	Amount	Shares	Amount				
Balances at December 31, 2018								
Cumulative effect adjustments from adoption of ASU 2016-02	169,244,520	\$ 17	384,366	\$ (4,585)	\$ 2,374,966	\$ (1,523)	\$ (1,178,769)	\$ 1,190,106
Issuance of ordinary shares - public offering	14,081,632	2	—	—	326,792	—	67	326,794
Issuance of ordinary shares in conjunction with the exercise of stock options and the vesting of restricted stock and performance stock units	4,227,998	—	—	—	24,881	—	—	24,881
Ordinary shares withheld for payment of employees' withholding tax liability	—	—	—	—	(31,569)	—	—	(31,569)
Issuance of ordinary shares in conjunction with Employee Share Purchase Plan	847,890	—	—	—	11,317	—	—	11,317
Share-based compensation	—	—	—	—	91,215	—	—	91,215
Currency translation adjustment	—	—	—	—	—	(382)	—	(382)
Net income	—	—	—	—	—	—	573,020	573,020
Balances at December 31, 2019	188,402,040	\$ 19	384,366	\$ (4,585)	\$ 2,797,602	\$ (1,905)	\$ (605,682)	\$ 2,185,449
Issuance of ordinary shares in conjunction with 2.5% Exchangeable Senior Notes due 2022	13,898,414	1	—	—	395,671	—	—	395,672
Issuance of ordinary shares - public offering	13,570,000	1	—	—	919,513	—	—	919,514
Issuance of ordinary shares in conjunction with the exercise of stock options and the vesting of restricted stock and performance stock units	5,109,168	1	—	—	36,869	—	—	36,870
Ordinary shares withheld for payment of employees' withholding tax liability	—	—	—	—	(66,505)	—	—	(66,505)
Issuance of ordinary shares in conjunction with Employee Share Purchase Plan	742,052	—	—	—	16,168	—	—	16,168
Share-based compensation	—	—	—	—	146,627	—	—	146,627
Currency translation adjustment	—	—	—	—	—	1,760	—	1,760
Net income	—	—	—	—	—	—	389,796	389,796
Balances at December 31, 2020	221,721,674	\$ 22	384,366	\$ (4,585)	\$ 4,245,945	\$ (145)	\$ (215,886)	\$ 4,025,351
Issuance of ordinary shares in conjunction with the exercise of stock options and the vesting of restricted stock and performance stock units	5,420,024	1	—	—	50,565	—	—	50,566
Issuance of ordinary shares in conjunction with Employee Share Purchase Plan	619,238	—	—	—	22,528	—	—	22,528
Ordinary shares withheld for payment of employees' withholding tax liability	—	—	—	—	(165,964)	—	—	(165,964)
Share-based compensation	—	—	—	—	220,263	—	—	220,263
Pension and other post-employment benefit plan remeasurements	—	—	—	—	—	(13,296)	—	(13,296)
Currency translation adjustment	—	—	—	—	—	(1,546)	—	(1,546)
Net income	—	—	—	—	—	—	534,491	534,491
Balances at December 31, 2021	227,760,936	\$ 23	384,366	\$ (4,585)	\$ 4,373,337	\$ (14,987)	\$ 318,605	\$ 4,672,393

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

HORIZON THERAPEUTICS PLC
CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	For the Years Ended December 31,		
	2021	2020	2019
CASH FLOWS FROM OPERATING ACTIVITIES:			
Net income	\$ 534,491	\$ 389,796	\$ 573,020
Adjustments to reconcile net income to net cash provided by operating activities:			
Depreciation and amortization expense	353,751	279,451	237,157
Equity-settled share-based compensation	219,086	146,627	91,215
Acquired in-process research and development expense	76,572	77,517	—
Impairment of long-lived asset	12,371	—	—
Amortization of debt discount and deferred financing costs	5,189	12,640	22,602
Loss on debt extinguishment	—	31,856	58,835
(Gain) loss on sale of assets	(2,000)	(4,883)	10,963
Deferred income taxes	(101,016)	(33,453)	(565,537)
Foreign exchange and other adjustments	(1,433)	1,812	574
Changes in operating assets and liabilities:			
Accounts receivable	34,796	(251,173)	56,166
Inventories	1,267	(21,451)	(3,268)
Prepaid expenses and other current assets	(88,193)	(114,788)	(72,763)
Accounts payable	(12,197)	16,015	(8,723)
Accrued trade discounts and rebates	(36,929)	(113,991)	8,591
Accrued expenses and other current liabilities	50,622	114,621	14,887
Other non-current assets and liabilities	(11,106)	25,092	2,613
Net cash provided by operating activities	1,035,271	555,688	426,332
CASH FLOWS FROM INVESTING ACTIVITIES:			
Payments for acquisitions, net of cash acquired	(2,845,275)	(262,305)	—
Purchases of property, plant and equipment	(76,596)	(169,852)	(17,857)
Payment related to license agreements	(49,572)	(30,000)	—
Payments for long-term investments, net	(24,668)	(13,314)	—
Proceeds from sale of assets	2,000	5,400	6,000
Change in escrow deposit for property purchase	—	6,000	(6,000)
Net cash used in investing activities	(2,994,111)	(464,071)	(17,857)
CASH FLOWS FROM FINANCING ACTIVITIES:			
Net proceeds from term loans	1,574,993	—	935,404
Repayment of term loans	(12,000)	—	(1,336,207)
Net proceeds from the issuance of senior notes	—	—	590,057
Repayment of senior notes	—	(1,739)	(814,420)
Proceeds from the issuance of ordinary shares in conjunction with Employee Share Purchase Plan	22,528	16,168	11,317
Proceeds from the issuance of ordinary shares in connection with stock option exercises	50,566	36,869	24,882
Payment of employee withholding taxes relating to share-based awards	(165,964)	(66,505)	(31,569)
Net proceeds from the issuance of ordinary shares	—	919,786	326,793
Contingent consideration proceeds from divestiture	—	—	3,297
Net cash provided by (used in) financing activities	1,470,123	904,579	(290,446)
Effect of foreign exchange rate changes on cash, cash equivalents and restricted cash	(10,606)	7,244	(107)
Net (decrease) increase in cash, cash equivalents and restricted cash	(499,323)	1,003,440	117,922
Cash, cash equivalents and restricted cash, beginning of the year	2,083,479	1,080,039	962,117
Cash, cash equivalents and restricted cash, end of the year	\$ 1,584,156	\$ 2,083,479	\$ 1,080,039

HORIZON THERAPEUTICS PLC
CONSOLIDATED STATEMENTS OF CASH FLOWS (CONTINUED)
(In thousands)

	For the Years Ended December 31,		
	2021	2020	2019
SUPPLEMENTAL CASH FLOW INFORMATION:			
Cash paid for interest	\$ 74,353	\$ 51,863	\$ 78,044
Cash paid for income taxes, net of refunds received	97,235	15,115	9,925
Cash paid for amounts included in the measurement of operating lease liabilities	8,868	7,840	6,484
SUPPLEMENTAL NON-CASH FLOW INFORMATION:			
Lease liabilities arising from obtaining right-of-use assets	\$ 62,156	\$ —	\$ 11,444
Purchases of acquired in-process research and development included in accrued expenses and other current liabilities	25,000	—	—
Purchases of property, plant and equipment included in accounts payable and accrued expenses and other current liabilities	9,228	13,430	117
Principal amount of 2.5% Exchangeable Senior Notes due 2022 converted into ordinary shares	—	398,261	—
Milestone payments for TEPEZZA intangible asset included in accrued expenses and other current liabilities	—	123,442	—

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

HORIZON THERAPEUTICS PLC
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS
December 31, 2021, 2020 and 2019

NOTE 1 – BASIS OF PRESENTATION AND BUSINESS OVERVIEW

Unless otherwise indicated or the context otherwise requires, references to “Horizon”, the “Company”, “we”, “us” and “our” refer to Horizon Therapeutics plc and its consolidated subsidiaries.

On March 15, 2021, the Company completed its acquisition of Viela Bio, Inc. (“Viela”) and acquired all of the issued and outstanding shares of Viela’s common stock for \$53.00 per share. The total consideration for the acquisition was approximately \$3.0 billion, including cash acquired of \$342.3 million. Following the completion of the acquisition, Viela became a wholly-owned subsidiary of the Company. The consolidated financial statements presented herein include the results of operations of the acquired business from the date of acquisition.

Business Overview

Horizon is focused on the discovery, development and commercialization of medicines that address critical needs for people impacted by rare, autoimmune and severe inflammatory diseases. The Company’s pipeline is purposeful: it applies scientific expertise and courage to bring clinically meaningful therapies to patients. Horizon believes science and compassion must work together to transform lives. The Company has two reportable segments, the orphan segment and the inflammation segment, and its commercial portfolio is currently composed of 12 medicines in the areas of rare diseases, gout, ophthalmology and inflammation.

As of December 31, 2021, the Company’s commercial portfolio consisted of the following medicines:

Orphan

TEPEZZA[®] (teprotumumab-trbw), for intravenous infusion
KRYSTEXXA[®] (pegloticase injection), for intravenous infusion
RAVICTI[®] (glycerol phenylbutyrate) oral liquid
PROCYSBI[®] (cysteamine bitartrate) delayed-release capsules and granules, for oral use
ACTIMMUNE[®] (interferon gamma-1b) injection, for subcutaneous use
UPLIZNA[®] (inebilizumab-cdon) injection, for intravenous use
BUPHENYL[®] (sodium phenylbutyrate) tablets and powder, for oral use
QUINSAIR[™] (levofloxacin) solution for inhalation

Inflammation

PENNSAID[®] (diclofenac sodium topical solution) 2% w/w (“PENNSAID 2%”), for topical use
DUEXIS[®] (ibuprofen/famotidine) tablets, for oral use
RAYOS[®] (prednisone) delayed-release tablets, for oral use
VIMOVO[®] (naproxen/esomeprazole magnesium) delayed-release tablets, for oral use

NOTE 2 – SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Basis of Presentation

The accompanying consolidated financial statements have been prepared in accordance with the accounting principles generally accepted in the United States of America (“GAAP”).

Principles of Consolidation

The consolidated financial statements include the Company’s accounts and those of its wholly owned subsidiaries. All intercompany accounts and transactions have been eliminated.

Segment Information

The Company’s reportable segments, which are the orphan segment and the inflammation segment, are reported in a manner consistent with the internal reporting provided to the Company’s chief operating decision maker (“CODM”). The Company’s CODM has been identified as its chief executive officer. The Company has no transactions between reportable segments.

Use of Estimates

The preparation of the accompanying consolidated financial statements in conformity with GAAP requires management to make certain estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent liabilities at the date of the financial statements and reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates.

Foreign Currency Translation and Transactions

The reporting currency of the Company and its subsidiaries is the U.S. dollar.

The U.S. dollar is the functional currency for the Company’s Ireland and United States-based businesses and the majority of its subsidiaries. The Company has foreign subsidiaries that have the Euro and the Canadian Dollar as their functional currency. Foreign currency-denominated assets and liabilities of these subsidiaries are translated into U.S. dollars based on exchange rates prevailing at the end of the period, revenues and expenses are translated at average exchange rates prevailing during the corresponding period, and shareholders’ equity accounts are translated at historical exchange rates as of the date of any equity transaction. The effects of foreign exchange gains and losses arising from the translation of assets and liabilities of those entities where the functional currency is not the U.S. dollar are included as a component of accumulated other comprehensive loss (“AOCI”).

Gains and losses resulting from foreign currency transactions are reflected within the Company’s results of operations.

Revenue Recognition

In the United States, the Company sells its medicines primarily to wholesale distributors and specialty pharmacy providers. In other countries, the Company sells its medicines primarily to wholesale distributors and other third-party distribution partners. These customers subsequently resell the Company’s medicines to health care providers and patients. In addition, the Company enters into arrangements with health care providers and payers that provide for government-mandated or privately negotiated discounts and allowances related to the Company’s medicines. Revenue is recognized when performance obligations under the terms of a contract with a customer are satisfied. The majority of the Company’s contracts have a single performance obligation to transfer medicines. Accordingly, revenues from medicine sales are recognized when the customer obtains control of the Company’s medicines, which occurs at a point in time, typically upon delivery to the customer. Revenue is measured as the amount of consideration the Company expects to receive in exchange for transferring medicines and is generally based upon a list or fixed price less allowances for medicine returns, rebates and discounts. The Company sells its medicines to wholesale pharmaceutical distributors and pharmacies under agreements with payment terms typically less than 90 days. The Company’s process for estimating reserves established for these variable consideration components does not differ materially from the Company’s historical practices.

Medicine Sales Discounts and Allowances

The nature of the Company's contracts gives rise to variable consideration because of allowances for medicine returns, rebates and discounts. Allowances for medicine returns, rebates and discounts are recorded at the time of sale to wholesale pharmaceutical distributors and pharmacies. The Company applies significant judgments and estimates in determining some of these allowances. If actual results differ from its estimates, the Company will be required to make adjustments to these allowances in the future. The Company's adjustments to gross sales are discussed further below.

Commercial Rebates

The Company participates in certain commercial rebate programs. Under these rebate programs, the Company pays a rebate to the commercial entity or third-party administrator of the program. The Company calculates accrued commercial rebate estimates using the expected value method. The Company accrues estimated rebates based on contract prices, estimated percentages of medicine that will be prescribed to qualified patients and estimated levels of inventory in the distribution channel and records the rebate as a reduction of revenue. Accrued commercial rebates are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Distribution Service Fees

The Company includes distribution service fees paid to its wholesalers for distribution and inventory management services as a reduction to revenue. The Company calculates accrued distribution service fee estimates using the most likely amount method. The Company accrues estimated distribution fees based on contractually determined amounts, typically as a percentage of revenue. Accrued distribution service fees are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Co-pay and Other Patient Assistance Programs

The Company offers discount card and other programs such as its HorizonCares program to patients under which the patient receives a discount on his or her prescription. In certain circumstances when a patient's prescription is rejected by a managed care vendor, the Company will pay for the full cost of the prescription. The Company reimburses pharmacies for this discount through third-party vendors. The Company reduces gross sales by the amount of actual co-pay and other patient assistance in the period based on invoices received. The Company also records an accrual to reduce gross sales for estimated co-pay and other patient assistance on units sold to distributors that have not yet been prescribed/dispensed to a patient. The Company calculates accrued co-pay and other patient assistance costs using the expected value method. The estimate is based on contract prices, estimated percentages of medicine that will be prescribed to qualified patients, average assistance paid based on reporting from the third-party vendors and estimated levels of inventory in the distribution channel. Accrued co-pay and other patient assistance costs are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Sales Returns

Consistent with industry practice, the Company maintains a return policy that allows customers to return certain medicines within a specified period prior to and subsequent to the medicine expiration date. Generally, medicines may be returned for a period beginning six months prior to its expiration date and up to one year after its expiration date. The right of return expires on the earlier of one year after the medicine expiration date or the time that the medicine is dispensed to the patient. The majority of medicine returns result from medicine dating, which falls within the range set by the Company's policy, and are settled through the issuance of a credit to the customer. The Company calculates sales returns using the expected value method. The estimate of the provision for returns is based upon the Company's historical experience with actual returns. The return period is known to the Company based on the shelf life of medicines at the time of shipment. The Company records sales returns in "accrued expenses and other current liabilities" and as a reduction of revenue.

Prompt Pay Discounts

As an incentive for prompt payment, the Company offers a 2% cash discount to most customers. The Company calculates accrued prompt pay discounts using the most likely amount method. The Company expects that all eligible customers will comply with the contractual terms to earn the discount. The Company records the discount as an allowance against "accounts receivable, net" and a reduction of revenue.

Government Rebates

The Company participates in certain government rebate programs such as Medicare Coverage Gap and Medicaid. The Company calculates accrued government rebate estimates using the expected value method. A significant portion of these accruals relates to the Company's Medicaid rebates. The Company accrues estimated rebates based on estimated percentages of medicine prescribed to qualified patients, estimated rebate percentages and estimated levels of inventory in the distribution channel that will be prescribed to qualified patients and records the rebates as a reduction of revenue. Accrued government rebates are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Chargebacks

The Company provides discounts to government qualified entities with whom the Company has contracted. These entities purchase medicines from the wholesale pharmaceutical distributors at a discounted price and the wholesale pharmaceutical distributors then charge back to the Company the difference between the current retail price and the contracted price that the entities paid for the medicines. The Company calculates accrued chargeback estimates using the expected value method. The Company accrues estimated chargebacks based on contract prices, sell-through sales data obtained from third-party information and estimated levels of inventory in the distribution channel and records the chargeback as a reduction of revenue. Accrued chargebacks are included in "accrued trade discounts and rebates" on the consolidated balance sheet.

Allowance for Credit Losses

The Company's medicines are sold to wholesale pharmaceutical distributors and pharmacies. The Company monitors its accounts receivable balances to determine the impact, if any, of such factors as changes in customer concentration, credit risk and the realizability of its accounts receivable, and records an allowance for credit losses when applicable.

Inventories

Inventories are stated at the lower of cost or net realizable value, using the first-in, first-out convention. Inventories consist of raw materials, work-in-process and finished goods. The Company has entered into manufacturing and supply agreements for the manufacture or purchase of raw materials and production supplies. The Company's inventories include the direct purchase cost of materials and supplies and manufacturing overhead costs. The Company reviews its inventory balance and purchase obligations to assess if it has obsolete or excess inventory and records a charge to "cost of goods sold" when applicable.

Inventories acquired in business combinations are recorded at their estimated fair values. "Step-up" represents the write-up of inventory from the lower of cost or net realizable value (the historical book value as previously recorded on the acquired company's balance sheet) to fair market value at the acquisition date. Inventory step-up expense is recorded in the consolidated statement of comprehensive income based on actual sales, or usage, using the first-in, first-out convention.

Inventories exclude medicine sample inventory, which is included in other current assets and is expensed as a component of "selling, general and administrative" expense when shipped to sales representatives.

Pre-launch Inventories

The Company capitalizes inventory costs associated with its medicine candidates prior to regulatory approval when, based on management judgment, future commercialization is considered probable and future economic benefit is expected to be realized. A number of factors are taken into consideration by management, including the current status of the regulatory approval process and any potential impediments to the approval process such as safety or efficacy. If future commercialization and future economic benefit is no longer considered probable, the capitalized pre-launch inventory would be expensed.

Cost of Goods Sold

The Company recognizes cost of goods sold in connection with its sales of each of its distributed medicines. Cost of goods sold includes all costs directly related to the acquisition of the Company's medicines from its third-party manufacturers, including freight charges and other direct expenses such as insurance and supply chain costs. Cost of goods sold also includes amortization of intellectual property as described in the intangible assets accounting policy below, inventory step-up expense, drug substance harmonization costs, share-based compensation, charges relating to discontinuation of clinical trials, royalty payments to third parties and loss on inventory purchase commitments.

Pre-clinical Studies and Clinical Trial Accruals

The Company's pre-clinical studies and clinical trials have historically been conducted by third-party contract research organizations and other vendors. Pre-clinical study and clinical trial expenses are based on the services received from these contract research organizations and vendors and are charged to R&D expense as incurred. Payments depend on factors such as the milestones accomplished, successful enrollment of certain numbers of patients and site initiation. In accruing service fees, the Company estimates the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from the estimate, the Company adjusts the accrual accordingly.

Net Income Per Share

Basic net income per share is computed by dividing net income by the weighted-average number of ordinary shares outstanding during the period. Diluted net income per share reflects the potential dilution beyond shares for basic net income per share that could occur if securities or other contracts to issue ordinary shares were exercised, converted into ordinary shares, or resulted in the issuance of ordinary shares that would have shared in the Company's earnings.

Cash and Cash Equivalents

The Company considers all highly liquid investments, readily convertible to cash, that mature within three months or less from date of purchase to be cash equivalents. Cash and cash equivalents primarily consist of cash balances and money market funds. The Company generally invests excess cash in money market funds and other financial instruments with short-term durations, based upon operating requirements.

Restricted Cash

Restricted cash consists primarily of balances in interest-bearing money market accounts required by a vendor for the Company's sponsored employee business credit card program and collateral for a letter of credit.

Fair Value of Financial Instruments

The carrying amounts of the Company's financial instruments, including cash and cash equivalents, restricted cash, accounts receivable, accounts payable and accrued expenses and other current liabilities, approximate their fair values due to their short maturities.

Investments

Investments consist primarily of equity securities, bank time deposits and money market funds. Investments in publicly traded equity securities are reported at fair value determined using quoted market prices in active markets. Changes in the fair value of these investments are included in other income (expense), net in the consolidated statement of comprehensive income.

Equity Method Investments

Investments in companies over which the Company has significant influence but not a controlling interest are accounted for using the equity method, with the share of earnings or losses reported in other income (expense), net.

Concentration of Credit Risk and Other Risks and Uncertainties

Financial instruments that potentially subject the Company to concentrations of credit risk consist of cash, cash equivalents and investments. The Company's investment policy permits investments in time deposits, U.S. federal government and federal agency securities, corporate bonds or commercial paper, money market instruments, certain qualifying money market mutual funds, certain repurchase agreements, and tax-exempt obligations of municipalities and places restrictions on credit ratings, maturities, and concentration by type and issuer. The Company is exposed to credit risk in the event of a default by the financial institutions holding the Company's cash, cash equivalents and investments to the extent recorded on the balance sheet.

The purchase cost of TEPEZZA drug substance, TEPEZZA drug product with the Company's recently approved second drug product manufacturer, Patheon Pharmaceuticals Inc. ("Patheon") (contract development and manufacturing organization services of Thermo Fisher Scientific), and ACTIMMUNE inventory are principally denominated in Euros and are subject to foreign currency risk. In addition, the Company is obligated to pay certain milestones and a royalty on sales of TEPEZZA to F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc. (together referred to as "Roche") in Swiss Francs, which obligations are subject to foreign currency risk. The Company has contracts relating to RAVICTI, QUINSAIR and PROCYSBI for sales in Canada which are subject to foreign currency risk. The Company also incurs certain operating expenses in currencies other than the U.S. dollar in relation to its Irish operations and foreign subsidiaries. Therefore, the Company is subject to volatility in cash flows due to fluctuations in foreign currency exchange rates, particularly changes in the Euro and the Swiss Franc. From time to time, the Company may enter into forward currency contracts to hedge its foreign currency risk exposure.

Historically, the Company's accounts receivable balances have been highly concentrated with a select number of customers consisting primarily of large wholesale pharmaceutical distributors who, in turn, sell the medicines to pharmacies, hospitals and other customers. As of December 31, 2021 and 2020, the Company's top four customers accounted for approximately 94% and 93%, respectively, of the Company's total outstanding accounts receivable balances. Given the size and creditworthiness of the customers, we have not experienced and do not expect to experience material credit related losses with such customers.

The Company depends on single-source suppliers and manufacturers for certain of its medicines, medicine candidates and their active pharmaceutical ingredients.

Business Combinations

The Company accounts for business combinations in accordance with the guidance in Accounting Standards Codification Topic 805, *Business Combinations* ("ASC 805") under which acquired assets and liabilities are measured at their respective estimated fair values as of the acquisition date. The Company may be required, as in the case of intangible assets, to determine the fair value associated with these amounts by estimating the fair value using an income approach under the discounted cash flow method, which may include revenue projections and other assumptions made by the Company to determine the fair value.

Provision for Income Taxes

The Company accounts for income taxes based upon an asset and liability approach. Deferred tax assets and liabilities represent the future tax consequences of the differences between the financial statement carrying amounts of assets and liabilities versus the tax basis of assets and liabilities. Under this method, deferred tax assets are recognized for deductible temporary differences, and operating loss and tax credit carryforwards. Deferred tax liabilities are recognized for taxable temporary differences. Deferred tax assets are reduced by a valuation allowance when, in the opinion of management, it is more likely than not that some portion or all of the deferred tax assets will not be realized. Significant judgment is required in determining whether it is probable that sufficient future taxable income will be available against which a deferred tax asset can be utilized. In determining future taxable income, the Company is required to make assumptions including the amount of taxable income in the various jurisdictions in which the Company operates. These assumptions require significant judgment about forecasts of future taxable income. Actual operating results in future years could render our current assumption of recoverability of deferred tax assets inaccurate. The impact of tax rate changes on deferred tax assets and liabilities is recognized in the period that the change is enacted. From time to time, the Company executes intercompany transactions in response to changes in operations, regulations, tax laws, funding needs and other circumstances. These transactions require the interpretation and application of tax laws in the applicable jurisdiction to support the tax treatment taken. The valuations which support the tax treatment of the transactions require significant estimates and assumptions within discounted cash flow models. The Company also accounts for the uncertainty in income taxes by utilizing a comprehensive model for the recognition, measurement, presentation and disclosure in financial statements of any uncertain tax positions that have been taken or are expected to be taken on an income tax return. Deferred tax assets and deferred tax liabilities are netted by each tax-paying entity within each jurisdiction on the Company's consolidated balance sheets.

Property, Plant and Equipment

Land is stated at cost. Property, plant and equipment, other than land, are stated at cost less accumulated depreciation. Depreciation is recognized using the straight-line method over the estimated useful lives of the related assets for financial reporting purposes and an accelerated method for income tax reporting purposes. Upon retirement or sale of an asset, the cost and related accumulated depreciation and amortization are removed from the balance sheet and the resulting gain or loss is reflected in operations. Repair and maintenance costs are charged to expenses as incurred and improvements are capitalized.

Leasehold improvements are amortized on a straight-line basis over the term of the applicable lease, or the useful life of the assets, whichever is shorter.

Depreciation and amortization periods for the Company's property, plant and equipment are as follows:

Buildings	40 years
Land improvements	10 years
Machinery and equipment	5 to 7 years
Furniture and fixtures	3 to 5 years
Computer equipment	3 years
Software	3 years
Trade show equipment	3 years

The Company capitalizes software development costs associated with internal use software, including external direct costs of materials and services and payroll costs for employees devoting time to a software project. Costs incurred during the preliminary project stage, as well as costs for maintenance and training, are expensed as incurred.

Software includes internal-use software acquired and modified to meet the Company's internal requirements. Amortization commences when the software is ready for its intended use.

Intangible Assets

Definite-lived intangible assets are amortized over their estimated useful lives. The Company reviews its intangible assets when events or circumstances may indicate that the carrying value of these assets is not recoverable and exceeds their fair value. The Company measures fair value based on the estimated future discounted cash flows associated with these assets in addition to other assumptions and projections that the Company deems to be reasonable and supportable. The estimated useful lives, from the date of acquisition, for all identified intangible assets that are subject to amortization are between five and thirteen years.

Indefinite-lived intangible assets consist of capitalized in-process research and development (“IPR&D”). IPR&D assets represent capitalized incomplete research projects that the Company acquired through business combinations. Such assets are initially measured at their acquisition date fair values and are tested for impairment, until completion or abandonment of research and development (“R&D”) efforts associated with the projects. An IPR&D asset is considered abandoned when R&D efforts associated with the asset have ceased, and there are no plans to sell or license the asset or derive value from the asset. At that point, the asset is considered to be impaired and is written off. Upon successful completion of each project, the Company will make a determination about the then remaining useful life of the intangible asset and begin amortization. The Company tests its indefinite-lived intangibles, including IPR&D assets, for impairment annually during the fourth quarter and more frequently if events or changes in circumstances indicate that it is more likely than not that the asset is impaired.

Goodwill

Goodwill represents the excess of the purchase price of acquired businesses over the estimated fair value of the identifiable net assets acquired. Goodwill is not amortized but is tested for impairment at least annually at the reporting unit level or more frequently if events or changes in circumstances indicate that the asset might be impaired. Impairment loss, if any, is recognized based on a comparison of the fair value of the asset to its carrying value, without consideration of any recoverability. The Company tests goodwill for impairment annually during the fourth quarter and whenever indicators of impairment exist by first assessing qualitative factors to determine whether it is more likely than not that the fair value is less than its carrying amount. If the Company concludes it is more likely than not that the fair value of a reporting unit is less than its carrying amount, a quantitative impairment test is performed. If the Company concludes that goodwill is impaired, it will record an impairment charge in its consolidated statement of comprehensive income.

R&D Expenses

R&D expenses include, but are not limited to, payroll and other personnel expenses, consultant expenses, expenses incurred under agreements with contract research organizations to conduct clinical trials, expenses incurred to manufacture clinical trial materials and acquired IPR&D assets. R&D expenses were \$432.0 million, \$209.4 million and \$103.2 million for the years ended December 31, 2021, 2020 and 2019, respectively.

Advertising Expenses

The Company expenses the costs of advertising as incurred. Advertising expenses were \$288.8 million, \$114.4 million and \$35.8 million for the years ended December 31, 2021, 2020 and 2019, respectively.

Deferred Financing Costs

Costs incurred in connection with debt financings have been capitalized to “Long-term debt, net” in the Company’s consolidated balance sheets as deferred financing costs, and are charged to interest expense using the effective interest method over the terms of the related debt agreements. These costs include document preparation costs, commissions, fees and expenses of investment bankers and underwriters, and accounting and legal fees.

Comprehensive Income

Comprehensive income is composed of net income and other comprehensive (loss) income (“OCI”). OCI includes certain changes in shareholders’ equity that are excluded from net income, which consist of foreign currency translation adjustments and pension and other post-employment benefit plan remeasurements. The Company reports the effect of significant reclassifications out of accumulated OCI on the respective line items in net income if the amount being reclassified is required under GAAP to be reclassified in its entirety to net income.

Share-Based Compensation

The Company accounts for employee share-based compensation by measuring and recognizing compensation expense for all share-based payments based on estimated grant date fair values. The Company uses the straight-line method to allocate compensation cost to reporting periods over each awardee's requisite service period, which is generally the vesting period. Forfeitures are estimated based on historical experience at the time of grant and revised in subsequent periods if actual forfeitures differ from those estimates.

Post-employment Benefits

The Company records annual expenses relating to its defined benefit U.S. retiree medical plan based on calculations which utilize various actuarial assumptions, including discount rates, health care cost trend rates, turnover rates, and retirement rates. The Company reviews its actuarial assumptions on an annual basis and makes modifications to the assumptions based on current rates and trends. Prior service costs and credits from plan amendments, including initiation of a plan, are deferred in AOCI, net of tax and amortized at an equal amount in each remaining year of service until the full eligibility date of employees active as of the amendment date. Actuarial gains and losses are deferred in AOCI, net of tax and amortized over the remaining service attribution periods of the employees under the corridor method.

Royalties

The Company records royalty expense based on each periods' net sales as part of cost of goods sold.

Leases

On January 1, 2019, the Company adopted Accounting Standards Update ("ASU") 2016-02, *Leases*. Under ASU No. 2016-02, an entity is required to recognize right-of-use lease assets and lease liabilities on its balance sheet and disclose key information about leasing arrangements. The Company adopted this standard on January 1, 2019, using a modified retrospective approach at the adoption date through a cumulative-effect adjustment to retained earnings. The Company applied the new guidance to all operating leases within the scope of the standard that were in effect on January 1, 2019, or entered into after, the adoption date. The adoption did not have a material impact on the Company's consolidated statement of comprehensive income. However, the new standard established \$38.0 million of liabilities and corresponding right-of-use assets of \$36.0 million on the Company's consolidated balance sheet for leases, primarily related to operating leases on rented office properties, that existed as of the January 1, 2019, adoption date.

The Company's leases primarily relate to operating leases of rented office properties. For contracts entered into on or after January 1, 2019, at the inception of a contract the Company assesses whether the contract is, or contains, a lease. The Company's assessment is based on: (1) whether the contract involves the use of a distinct identified asset, (2) whether the Company obtains the right to substantially all the economic benefit from the use of the asset throughout the period, and (3) whether the Company has the right to direct the use of the asset. At inception of a lease, the Company allocates the consideration in the contract to each lease component based on its relative stand-alone price to determine the lease payments.

For leases with terms greater than 12 months, the Company records the related asset and obligation at the present value of lease payments over the term. The right-of-use lease asset represents the right to use the leased asset for the lease term. The lease liability represents the present value of the lease payments under the lease.

The right-of-use lease asset is initially measured at cost, which primarily comprises the initial amount of the lease liability, plus any initial direct costs incurred. All right-of-use lease assets are reviewed for impairment. The lease liability is initially measured at the present value of the lease payments, discounted using the interest rate implicit in the lease or, if that rate cannot be readily determined, the Company's secured incremental borrowing rate for the same term as the underlying lease.

The Company identified and assessed the following significant assumptions in recognizing the right-of-use lease assets and corresponding liabilities.

Expected lease term – The expected lease term includes both contractual lease periods and, when applicable, cancelable option periods. When determining the lease term, the Company includes options to extend or terminate the lease when it is reasonably certain that the Company will exercise that option.

Incremental borrowing rate – As the Company’s leases do not provide an implicit rate, the Company obtained the incremental borrowing rate (“IBR”) based on the remaining term of each lease. The IBR is the rate of interest that a lessee would have to pay to borrow on a collateralized basis over a similar term an amount equal to the lease payments in a similar economic environment.

The Company has elected not to recognize right-of-use lease assets and lease liabilities for short-term leases that have a term of 12 months or less.

The Company reports right-of-use lease assets within non-current “Other assets” in its consolidated balance sheet. The Company reports the current portion of lease liabilities within “Accrued expenses and other current liabilities” and long-term lease liabilities within “Other long-term liabilities” in its consolidated balance sheet.

Contingencies

From time to time, the Company may become involved in claims and other legal matters arising in the ordinary course of business. The Company records accruals for loss contingencies to the extent that it concludes 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.

Recent Accounting Pronouncements

From time to time, the Company adopts new accounting pronouncements issued by the Financial Accounting Standards Board (“FASB”) or other standard-setting bodies.

In December 2019, the FASB issued Accounting Standards Update No. 2019-12, *Income Taxes (Topic 740): Simplification and reduce the cost of accounting for income taxes* (“ASU 2019-12”), which was effective for the Company as of January 1, 2021. The adoption of ASU 2019-12 did not have a material impact on the Company’s consolidated financial statements and related disclosures.

Other recent authoritative guidance issued by the FASB (including technical corrections to the Accounting Standards Codification (“ASC”)), the American Institute of Certified Public Accountants and the Securities and Exchange Commission (“SEC”) did not, or are not expected to, have a material impact on the Company’s consolidated financial statements and related disclosures.

NOTE 3 – NET INCOME PER SHARE

The following table presents basic and diluted net income per share for the years ended December 31, 2021, 2020 and 2019 (in thousands, except share and per share data):

	For the Years Ended December 31,		
	2021	2020	2019
Basic net income per share calculation:			
Numerator - net income	\$ 534,491	\$ 389,796	\$ 573,020
Denominator - weighted average of ordinary shares outstanding	225,551,410	203,967,246	182,930,109
Basic net income per share	\$ 2.37	\$ 1.91	\$ 3.13
Diluted net income per share calculation:			
Net income	\$ 534,491	\$ 389,796	\$ 573,020
Effect of assumed conversion of 2.50% Exchangeable Senior Notes due 2022, net of tax	—	—	22,440
Numerator - net income	\$ 534,491	\$ 389,796	\$ 595,460
Denominator - weighted average of ordinary shares outstanding	235,680,483	215,308,768	205,224,221
Diluted net income per share	\$ 2.27	\$ 1.81	\$ 2.90

Basic net income per share is computed by dividing net income by the weighted-average number of ordinary shares outstanding during the period. Diluted net income per share reflects the potential dilution that could occur if securities or other contracts to issue ordinary shares were exercised, converted into ordinary shares, or resulted in the issuance of ordinary shares that would have shared in the Company's earnings.

During the years ended December 31, 2021, 2020 and 2019, the difference between the basic and diluted weighted average ordinary shares outstanding primarily represents the effect of incremental shares from the Company's share-based compensation programs.

The outstanding securities listed in the table below were excluded from the computation of diluted net income per ordinary share for the years ended December 31, 2021, 2020 and 2019 due to being anti-dilutive:

	For the Years Ended December 31,		
	2021	2020	2019
Stock options	397,576	44,670	233,260
Restricted stock units	1,557,405	2,398,710	1,840
Performance stock units	791,747	790,949	586,868
Employee share purchase plan shares	295,050	18,618	2,207
2.50% Exchangeable Senior Notes due 2022	—	6,862,376	—
	3,041,778	10,115,323	824,175

Beginning in the fourth quarter of 2019, with the Company's ordinary share price significantly above the \$28.66 exchange price, the Company decided that it no longer had the intent to settle the Company's 2.50% Exchangeable Senior Notes due 2022 (the "Exchangeable Senior Notes") for cash and, as a result, began to prospectively apply the if-converted method to the Exchangeable Senior Notes when determining the diluted net income per share. By August 3, 2020, the Exchangeable Senior Notes were fully extinguished through exchanges for ordinary shares or cash redemption.

NOTE 4 –ACQUISITIONS, DIVESTITURES AND OTHER ARRANGEMENTS

Acquisition of biologic drug product manufacturing facility

In July 2021, the Company completed the purchase of a biologic drug product manufacturing facility from EirGen Pharma Limited (“EirGen”), a subsidiary of OPKO Health, Inc. in Waterford, Ireland for \$67.9 million, which included an upfront cash payment of \$64.8 million and \$3.1 million of additional transaction costs, legal fees and liabilities assumed. The facility, which is located in an Industrial Development Agency Ireland (“IDA Ireland”) business park, includes a filling line and lyophilizer, or freeze dryer, that can be used for both the Company’s commercial medicines, including its rare disease biologics TEPEZZA, KRYSTEXXA and UPLIZNA, and certain of its medicine candidates in development, following build-out, validation and regulatory approval processes. In addition, there is adjacent IDA Ireland land available for further manufacturing and development expansion. The Company accounted for the transaction as an asset acquisition.

The following table summarizes fair values of assets acquired as of the acquisition date (in thousands):

Construction in process	\$	22,736
Buildings		21,550
Furniture and fixtures		1,089
Definite-lived intangible assets		21,794
Other		775
Total consideration	\$	67,944

Acquisition of Viela

On March 15, 2021, the Company completed its acquisition of Viela and acquired all of the issued and outstanding shares of Viela’s common stock for \$53.00 per share. The acquisition added an additional rare disease medicine, UPLIZNA, to the Company’s commercial medicine portfolio. The Viela acquisition also provides multiple opportunities to drive long-term growth and solidify the Company’s future as an innovation-driven biotech company. Viela’s mid-stage biologics pipeline, R&D team and on-market medicine UPLIZNA, made it a complementary strategic fit with the Company’s pipeline, commercial portfolio and therapeutic areas of focus. Following completion of the acquisition, Viela became a wholly-owned subsidiary of the Company. The Company financed the transaction through cash on hand and \$1.6 billion of aggregate principal amount of term loans pursuant to the Company’s existing credit agreement, as described in Note 13.

The total consideration for the acquisition was approximately \$3.0 billion, including cash acquired of \$342.3 million, and was composed of the following (in thousands):

Equity value (54,988,820 shares at \$53.00 per share)	\$	2,914,407
Net settlements on the exercise of stock options		78,554
Consideration for exchange of Viela stock options		1,130
Total consideration	\$	2,994,091

During the year ended December 31, 2021, the Company incurred \$28.6 million in Viela transaction costs, including advisory, legal, accounting, valuation and other professional and consulting fees, which were accounted for as “Selling, General and Administrative Expenses” in the consolidated statement of comprehensive income.

Pursuant to ASC 805, the Company accounted for the Viela acquisition as a business combination using the acquisition method of accounting. Identifiable assets and liabilities of Viela, including identifiable intangible assets, were recorded based on their estimated fair values as of the date of the closing of the acquisition. The excess of the purchase price over the fair value of the net assets acquired was recorded as goodwill. While all amounts were subject to adjustments, the areas subject to the most significant potential adjustments were inventory, intangible assets, IPR&D and deferred income taxes. As a result, the Company recorded preliminary estimates for the fair value of assets acquired and liabilities assumed as of the acquisition date. Such preliminary valuation required estimates and assumptions including, but not limited to, estimating future cash flows and direct costs in addition to developing the appropriate discount rates and current market profit margins. The Company’s management believes the fair values recognized for the assets acquired and the liabilities assumed are based on reasonable estimates and assumptions.

During the year ended December 31, 2021, the Company recorded measurement period adjustments related to deferred tax liabilities, accrued expenses and other current liabilities, accrued trade discounts and rebates, accounts receivable, prepaid expenses and other current assets and inventory, which resulted in a net reduction in goodwill of \$9.7 million.

The following table summarizes the fair values assigned to the assets acquired and the liabilities assumed by the Company along with the resulting goodwill before and after the measurement period adjustments (in thousands):

	Before	Adjustments	After
Deferred tax liabilities, net	\$ (457,928)	\$ 6,589	\$ (451,339)
Accrued expenses and other current liabilities	(73,401)	(335)	(73,736)
Other long-term liabilities	(22,631)	—	(22,631)
Accounts payable	(4,768)	—	(4,768)
Accrued trade discounts and rebates	(1,492)	(373)	(1,865)
Marketable securities	400	—	400
Property, plant and equipment	1,747	—	1,747
Other assets	3,253	1,613	4,866
Accounts receivable	8,053	(267)	7,786
Prepaid expenses and other current assets	16,444	152	16,596
Inventories	149,348	2,300	151,648
Cash and cash equivalents	342,347	—	342,347
In-process research and development	910,000	—	910,000
Developed technology	1,460,000	—	1,460,000
(Liabilities assumed) and assets acquired	2,331,372	9,679	2,341,051
Goodwill	662,719	(9,679)	653,040
Fair value of consideration paid	\$ 2,994,091	\$ —	\$ 2,994,091

Inventories acquired included raw materials, work in process and finished goods for UPLIZNA. Inventories were recorded at their estimated fair values. The fair value of finished goods has been determined based on the estimated selling price, net of selling costs and a margin on the selling activities. The fair value of work in process has been determined based on estimated selling price, net of selling costs and costs to complete the manufacturing, and a margin on the selling and manufacturing activities. The fair value of raw materials was estimated to equal the replacement cost. A step-up in the value of inventory of \$149.3 million was originally recorded in connection with the acquisition, which was composed of \$10.1 million for raw materials, \$119.0 million for work-in-process and \$20.2 million for finished goods. During the year ended December 31, 2021, the step-up in the value of inventory was increased to \$151.6 million following the recording of \$2.3 million in measurement period adjustments which was composed of \$1.9 million for work-in-process and \$0.4 million for finished goods. During the year ended December 31, 2021, the Company recorded inventory step-up expense of \$27.6 million related to UPLIZNA based on the acquired units sold during the period.

Other tangible assets and liabilities were valued at their respective carrying amounts as management believes that these amounts approximated their acquisition-date fair values.

Developed technology is an intangible asset that reflects the estimated fair value of the rights to UPLIZNA in the United States. The estimated fair values of the developed technology represent valuations performed with the assistance of an independent appraisal firm based on management's estimates, forecasted financial information and reasonable and supportable assumptions. The fair value of developed technology was determined using an income approach. The income approach explicitly 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 for UPLIZNA. Indications of value were developed by discounting these benefits to their acquisition-date fair value at a discount rate of 11.5% that reflects the return requirements of the market. Some of the most significant assumptions inherent in the development of the asset valuation include the estimated net cash flows for each year (including net sales, cost of goods sold, sales and marketing costs and R&D costs) and the discount rate. The fair value of the UPLIZNA developed technology was capitalized as of the Viela acquisition date and is subsequently being amortized over approximately 14 years.

IPR&D is related to R&D projects including:

- (i) Potential regulatory approval of UPLIZNA for neuromyelitis optica spectrum disorder (“NMOSD”) outside of the United States and certain other indications worldwide. As of the date of the acquisition, UPLIZNA had not been granted regulatory approval in any territory outside the United States or for any indications other than NMOSD in the United States. On March 23, 2021, the Company’s strategic partner, Mitsubishi Tanabe Pharma Corporation, received manufacturing and marketing approval for UPLIZNA in Japan. Refer to Note 8 for further details.
- (ii) Daxdilimab (HZN-7734), an investigational human monoclonal antibody designed to deplete plasmacytoid dendritic cells (pDCs), a cell type believed to be critical to the pathogenesis of multiple autoimmune diseases.
- (iii) Dazodalibep (HZN-4920), an investigational fusion protein designed to block a key co-stimulatory pathway involved in many autoimmune and inflammatory diseases.

Each IPR&D asset is considered separable from the business as each project could be sold to a third party. The fair value of each IPR&D asset was determined using an income approach. The income approach explicitly 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 sales projections and estimated direct costs. Indications of value are developed by discounting these benefits to their present value at a discount rate of 12.5% that reflects the return requirements of the market. Some of the most significant assumptions inherent in the development of the asset valuations include the estimated net cash flows for each year (including net sales, cost of goods sold, sales and marketing costs and R&D costs), the discount rate, the assessment of each asset’s life cycle and the potential regulatory and commercial success risk. The fair value of the various IPR&D assets was recorded as an indefinite-lived intangible asset and will be tested for impairment until completion or abandonment of R&D efforts associated with the project. The Company reviews amounts capitalized as acquired IPR&D for impairment annually and whenever events or changes in circumstances indicate that the carrying value of the assets might not be recoverable.

Deferred tax assets and liabilities arise from acquisition accounting adjustments where book values of certain assets and liabilities differ from their tax bases. Deferred tax assets and liabilities are recorded at the currently enacted rates which will be in effect at the time when the temporary differences are expected to reverse in the country where the underlying assets and liabilities are located. The developed technology, IPR&D assets and inventory acquired through the Viela acquisition were located in the United States as of the acquisition date, where a U.S. tax rate of 23.8% is being utilized and a significant deferred tax liability of \$451.3 million was recorded.

Goodwill represents the excess of the total consideration over the estimated fair value of net assets acquired and was recorded in the consolidated balance sheet as of the acquisition date. The goodwill was primarily attributable to the establishment of a deferred tax liability for the developed technology intangible asset and the IPR&D intangible assets. Viela’s mid-stage biologics pipeline, R&D team and on-market medicine UPLIZNA, made it a complementary strategic fit with the Company’s pipeline, commercial portfolio and therapeutic areas of focus. The Company does not expect any portion of this goodwill to be deductible for tax purposes.

The following table presents the pro forma combined results of the Company and Viela for the year ended December 31, 2021 and 2020 as if the acquisition of Viela had occurred on January 1, 2020 (in thousands):

	For the Year Ended December 31,					
	2021			2020		
	As reported	Pro forma adjustments	Pro forma	As reported	Pro forma adjustments	Pro forma
Net sales	\$3,226,410	\$ 10,588	\$3,236,998	\$2,200,429	\$ 11,652	\$2,212,081
Net income	534,491	(30,804)	503,687	389,796	(291,730)	98,066

The pro forma combined financial information was prepared using the acquisition method of accounting and was based on the historical financial information of the Company and Viela. In order to reflect the pro forma information as if the acquisition occurred on January 1, 2020 as required, the pro forma financial information includes adjustments to reflect incremental amortization expense to be incurred based on the current fair values of the identifiable intangible assets acquired; the incremental cost of products sold related to the fair value adjustments associated with acquisition date inventory; the additional interest expense associated with the issuance of debt to finance the acquisition; and the reclassification of transaction costs incurred during the year ended December 31, 2021 to the year ended December 31, 2020. Significant non-recurring pro forma adjustments include transaction costs of \$86.6 million which were assumed to have been incurred on January 1, 2020 and were recognized as if incurred during the year ended December 31, 2020. The pro forma financial information is not necessarily indicative of what the consolidated results of operations would have been had the acquisition actually been completed on January 1, 2020. In addition, the pro forma financial information is not a projection of future results of operations of the combined company nor does it reflect the expected realization of any synergies or cost savings associated with the acquisition.

Acquisition of Curzion Pharmaceuticals, Inc.

On April 1, 2020, the Company acquired Curzion Pharmaceuticals, Inc. (“Curzion”), a privately held development-stage biopharma company, and its development-stage oral selective lysophosphatidic acid 1 receptor (LPA₁) antagonist, CZN001 (renamed HZN-825).

Under the terms of the acquisition agreement, the Company acquired Curzion for a \$45.0 million upfront cash payment with additional payments contingent on the achievement of development and regulatory milestones. Pursuant to ASC 805 (as amended by ASU No. 2017-01, *Business Combinations (Topic 805): Clarifying the Definition of a Business* (“ASU No. 2017-01”)), the Company accounted for the Curzion acquisition as the purchase of an IPR&D asset and, pursuant to ASC Topic 730, *Research and Development* (“ASC 730”), recorded the purchase price as R&D expense during the year ended December 31, 2020. HZN-825 was originally discovered and developed by Sanofi-Aventis U.S. LLC, which is eligible to receive contingent payments upon the achievement of development and commercialization milestones and royalties based on revenue thresholds. A member of the Company’s board of directors was also a member of the board of directors of, and held a beneficial interest in, Curzion. This related party transaction was conducted in the normal course of business on an arm’s length basis.

Sale of RAVICTI and BUPHENYL Rights in Japan

On October 27, 2020, the Company sold its rights to develop and commercialize RAVICTI and BUPHENYL in Japan to Medical Need Europe AB, part of the Immedica Group, for \$5.4 million and recorded a gain of \$4.9 million on the sale in the fourth quarter of 2020. The Company has retained the rights to RAVICTI and BUPHENYL in North America.

Sale of MIGERGOT rights

On June 28, 2019, the Company sold its rights to MIGERGOT to Cosette Pharmaceuticals, Inc., for \$6.0 million and total potential contingent consideration payments of \$4.0 million (the “MIGERGOT transaction”).

Pursuant to ASU No. 2017-01, the Company accounted for the MIGERGOT transaction as a sale of assets, specifically a sale of intellectual property rights, and a sale of inventory.

The loss on sale of assets recorded to the consolidated statement of comprehensive income during the year ended December 31, 2019, was determined as follows (in thousands):

Cash proceeds	\$	6,000
Less net assets sold:		
Developed technology		(16,999)
Inventory		(236)
Release of contingent consideration liability		272
Loss on sale of assets	\$	(10,963)

Acquisition of River Vision

On May 8, 2017, the Company acquired 100% of the equity interests in River Vision Development Corp. (“River Vision”) for upfront cash payments totaling approximately \$150.3 million, including cash acquired of \$6.3 million, with additional potential future milestone and royalty payments contingent on the satisfaction of certain regulatory milestones and sales thresholds. Pursuant to ASU No. 2017-01, the Company accounted for the River Vision acquisition as the purchase of an IPR&D asset (teprotumumab, now known as TEPEZZA) and, pursuant to ASC 730, recorded the purchase price as R&D expense during the year ended December 31, 2017.

Under the acquisition agreement for River Vision, the Company agreed to pay up to \$325.0 million upon the attainment of various milestones, composed of \$100.0 million related to U.S. Food and Drug Administration (“FDA”) approval and \$225.0 million related to net sales thresholds for TEPEZZA. The agreement also includes a royalty payment of 3 percent of the portion of annual worldwide net sales exceeding \$300.0 million. The Company made the milestone payment of \$100.0 million related to FDA approval during the first quarter of 2020 which is now capitalized as a finite-lived intangible asset representing the developed technology for TEPEZZA.

Additionally, under the Company’s license agreement with Roche, the Company made a milestone payment of CHF5.0 million (\$5.2 million when converted using a CHF-to-Dollar exchange rate at the date of payment of 1.0382), during the first quarter of 2020 which the Company also capitalized as a finite-lived intangible asset representing the developed technology for TEPEZZA.

In April 2020, a subsidiary of the Company entered into an agreement with S.R. One, Limited (“S.R. One”) and an agreement with Lundbeckfond Invest A/S (“Lundbeckfond”) pursuant to which the Company acquired all of S.R. One’s and Lundbeckfond’s beneficial rights to proceeds from certain contingent future TEPEZZA milestone and royalty payments in exchange for a one-time payment of \$55.0 million to each of the respective parties. The total payments of \$110.0 million were capitalized as a finite-lived intangible asset representing the developed technology for TEPEZZA during the second quarter of 2020.

In addition, during the year ended December 31, 2020, the Company recorded \$120.8 million as a finite-lived intangible asset representing the developed technology for TEPEZZA, composed of \$67.0 million in relation to the expected future attainment of various net sales milestones payable under the acquisition agreement for River Vision and CHF50.0 million (\$53.8 million when converted using a CHF-to-Dollar exchange rate as of the date the intangible asset was recorded) in relation to the expected future attainment of various net sales milestones payable to Roche. The liabilities relating to these TEPEZZA net sales milestones were recorded in accrued expenses and other current liabilities on the consolidated balance sheet as of December 31, 2020. The Company paid such TEPEZZA net sales milestones to Roche in February 2021 and to the former River Vision stockholders in April 2021 and, following such payments, there are no further TEPEZZA net sales milestone obligations remaining to Roche and the former River Vision stockholders. The Company’s remaining obligation to Roche relating to the attainment of various TEPEZZA development and regulatory milestones is CHF43.0 million (\$47.0 million when converted using a CHF-to-Dollar exchange rate at December 31, 2021 of 1.0937).

Refer to Note 15 for further detail on TEPEZZA milestone payments.

Other Arrangements

Alpine Immune Sciences, Inc.

On December 15, 2021, the Company entered into an exclusive license agreement with Alpine Immune Sciences, Inc. (“Alpine”) for the development and commercialization of up to four preclinical candidates generated from Alpine’s unique discovery platform. The agreement includes licensing of a lead, potential first-in-class preclinical candidate, as well as a research partnership to jointly generate additional novel candidates. These candidates include previously undisclosed multi-specific fusion protein-based therapeutic candidates for autoimmune and inflammatory diseases.

In connection with the execution of the license agreement, the Company entered into a stock purchase agreement with Alpine to purchase a minority stake of 951,980 shares of Alpine’s common stock in a private placement.

Under the terms of the agreements, the Company paid Alpine \$15.0 million in the fourth quarter of 2021 and paid \$25.0 million in the first quarter of 2022. The shares of Alpine's common stock were purchased at a premium to their fair value at the transaction closing date. The premium consisted of acquiring the shares at a price above the fair value based on a premium to the 30-day volume-weighted average share price prior to entering into the agreement. The Company recorded an asset of \$11.9 million in other assets in our consolidated balance sheet reflecting the fair value of the common stock. In addition, we recorded a charge of \$28.1 million to R&D expense in our consolidated statement of comprehensive income for the year ended December 31, 2021, of which \$25.0 million relates to the upfront payment and \$3.1 million relates to the premium paid for shares of Alpine's common stock. The \$28.1 million was accounted for as the acquisition of an IPR&D asset during the year ended December 31, 2021.

In addition, Alpine is eligible to receive up to \$381.0 million per program, or approximately \$1.52 billion in total, in future success-based payments related to development, regulatory and commercial milestones. Additionally, Alpine is eligible to receive tiered royalties from a mid-single digit percentage to a low double-digit percentage on global net sales. Alpine will advance candidate molecules to pre-defined preclinical milestones, and the Company will be responsible for the costs. The Company will then assume responsibility for development and commercialization activities and costs.

Arrowhead Pharmaceuticals, Inc.

On June 18, 2021, the Company entered into a global agreement with Arrowhead Pharmaceuticals, Inc. ("Arrowhead") for ARO-XDH, a previously undisclosed discovery-stage investigational RNA interference ("RNAi") therapeutic being developed by Arrowhead as a potential treatment for uncontrolled gout. Arrowhead granted the Company a worldwide exclusive license to develop, manufacture and commercialize products based on the RNAi therapeutic. Arrowhead will conduct all research and preclinical development activities for the RNAi therapeutic products. The Company must use commercially reasonable efforts in, and will be responsible for, clinical development and commercialization of the RNAi therapeutic products. Under the terms of the agreement, the Company paid Arrowhead an upfront cash payment of \$40.0 million in July 2021 and agreed to pay additional potential future milestone payments of up to \$660.0 million contingent on the achievement of certain development, regulatory and commercial milestones, and low to mid-teens royalties on worldwide calendar year net sales of licensed products. The \$40.0 million upfront payment was accounted for as the acquisition of an IPR&D asset and was recorded as a R&D expense in the consolidated statement of comprehensive income during the year ended December 31, 2021.

Halozyme Therapeutics, Inc.

On November 21, 2020, the Company entered into a global agreement with Halozyme Therapeutics, Inc. ("Halozyme") that gives the Company exclusive access to Halozyme's ENHANZE[®] drug delivery technology for subcutaneous ("SC") formulation of medicines targeting IGF-1R. The Company is using ENHANZE to develop a SC formulation of TEPEZZA, indicated for the treatment of thyroid eye disease, a serious, progressive and vision-threatening rare autoimmune disease, potentially shortening drug administration time, reducing healthcare practitioner time and offering additional flexibility and convenience for patients. Under the terms of the agreement, the Company paid Halozyme an upfront cash payment of \$30.0 million in December 2020, with additional potential future milestone payments of up to \$160.0 million contingent on the satisfaction of certain development and sales thresholds. Halozyme will also be entitled to receive mid-single digit royalties on sales of commercialized medicines using the ENHANZE technology. The \$30.0 million upfront payment was accounted for as the acquisition of an IPR&D asset and was recorded as a R&D expense in the consolidated statement of comprehensive income during the year ended December 31, 2020.

HemoShear Therapeutics, LLC

On January 3, 2019, the Company entered into an agreement with HemoShear Therapeutics, LLC ("HemoShear"), a biotechnology company, to discover novel therapeutic targets for gout. The agreement provides the Company with an opportunity to address unmet treatment needs for people with gout by evaluating new targets for the control of serum uric acid levels. Under the terms of the agreement, the Company paid HemoShear an upfront cash payment of \$2.0 million with additional potential future milestone payments upon commencement of new stages of development, contingent on the Company's approval at each stage. In June 2019, a \$4.0 million progress payment became due, which the Company subsequently paid in July 2019. In June 2020, a \$3.0 million progress payment became due, which the Company subsequently paid in July 2020. Progress payments of \$7.0 million became due and were paid during the year ended December 31, 2021.

NOTE 5 – INVENTORIES

The components of inventories as of December 31, 2021 and 2020 consisted of the following (in thousands):

	As of December 31,	
	2021	2020
Raw materials	\$ 43,366	\$ 11,760
Work-in-process	101,719	33,167
Finished goods	80,645	30,356
Inventories, net	\$ 225,730	\$ 75,283

During the year ended December 31, 2021, as part of the Viela acquisition, a step-up in the value of inventory of \$151.6 million was recorded, which was composed of \$10.1 million for raw materials, \$120.9 million for work-in-process and \$20.6 million for finished goods. Refer to Note 4 for further details. The Company recorded \$27.6 million of UPLIZNA inventory step-up expense in cost of goods sold during the year ended December 31, 2021.

Because inventory step-up expense is related to an acquisition, will not continue indefinitely and has a significant effect on the Company's gross profit, gross margin percentage and net loss for all affected periods, the Company discloses balance sheet and income statement amounts related to inventory step-up within the Notes to Consolidated Financial Statements.

NOTE 6 – PREPAID EXPENSES AND OTHER CURRENT ASSETS

Prepaid expenses and other current assets as of December 31, 2021 and 2020 consisted of the following (in thousands):

	As of December 31,	
	2021	2020
Advance payments for inventory	\$ 160,103	\$ 137,680
Deferred charge for taxes on intercompany profit	66,175	52,306
Prepaid income taxes and income tax receivable	36,388	102
Rabbi trust assets	26,519	18,423
Other prepaid expenses and other current assets	67,921	43,434
Prepaid expenses and other current assets	\$ 357,106	\$ 251,945

Advance payments for inventory as of December 31, 2021 and 2020, primarily represented payments made to the contract manufacturer of TEPEZZA drug substance.

NOTE 7 – PROPERTY, PLANT AND EQUIPMENT

Property, plant and equipment as of December 31, 2021 and 2020 consisted of the following (in thousands):

	As of December 31,	
	2021	2020
Buildings	\$ 174,209	\$ 80,341
Land and land improvements	40,468	38,076
Construction in process	28,210	63,656
Leasehold improvements	23,801	26,323
Furniture and fixtures	19,318	5,973
Machinery and equipment	18,390	4,695
Software	13,388	14,618
Other	10,418	3,146
	328,202	236,828
Less accumulated depreciation	(35,904)	(47,791)
Property, plant and equipment, net	\$ 292,298	\$ 189,037

Depreciation expense for the years ended December 31, 2021, 2020 and 2019 was \$17.5 million, \$24.3 million and \$6.7 million, respectively.

In July 2021, the Company completed the purchase of a biologic drug product manufacturing facility from EirGen. Refer to Note 4 for further details.

In February 2020, the Company purchased a three-building campus in Deerfield, Illinois for total consideration and directly attributable transaction costs of \$118.5 million. The Deerfield campus totals 70 acres and consists of approximately 650,000 square feet of office space. The Company's office employees previously located in Lake Forest, Illinois moved to the Deerfield campus in February 2021. In January 2022, the Company entered into a sublease agreement for the entire Lake Forest office building for the remaining term of the original lease through March 31, 2031. The increase in amount classified as buildings and the decrease in amount classified as construction in process is primarily due to the Deerfield campus becoming operational in February 2021.

NOTE 8 – GOODWILL AND INTANGIBLE ASSETS

Goodwill

The table below presents goodwill for the Company's reportable segments as of December 31, 2021 (in thousands):

	Orphan	Inflammation	Total
Balance at December 31, 2020	\$ 357,498	\$ 56,171	\$ 413,669
Goodwill recognized on acquisition of Viela	662,719	—	662,719
Adjustment relating to the acquisition of Viela	(9,679)	—	(9,679)
Balance at December 31, 2021	<u>\$ 1,010,538</u>	<u>\$ 56,171</u>	<u>\$ 1,066,709</u>

In March 2021, the Company recognized goodwill with a preliminary value of \$662.7 million in connection with the Viela acquisition, which represented the excess of the purchase price over the fair value of the net assets acquired. During the year ended December 31, 2021, the Company recorded measurement period adjustments related to deferred tax liabilities, accounts receivable, prepaid expenses and other current assets, accrued expenses and other current liabilities and accrued trade discounts and rebates, which resulted in a net decrease in goodwill of \$9.7 million, to \$653.0 million. Refer to Note 4 for further details.

As of December 31, 2021, there were no accumulated goodwill impairment losses.

At September 30, 2021, the Company determined that there was an indicator to trigger an interim impairment analysis of the inflammation reporting unit's goodwill. The indicator was the August 2021 launch of a generic version of DUEXIS in the United States, resulting in a decrease in future expected net sales. As of September 30, 2021, the Company performed a quantitative assessment to determine if it was more likely than not that the fair value of the inflammation reporting unit exceeds its carrying value, including goodwill. The fair value of the inflammation reporting unit exceeded its carrying value by more than 30%, resulting in no impairment.

The Company determined the fair value of the inflammation reporting unit using accepted valuation methods, including the use of discounted cash flows that incorporate the use of projected financial information and a 7% discount rate developed using market participant-based assumptions. The cash-flow projections are based on a five-year financial forecast developed by management that includes net sales projections, which are updated annually and reviewed by management. The selected discount rate considered the risk and nature of the inflammation reporting unit's cash flows and the rates of return market participants would require to invest their capital in the Company's reporting unit.

In addition, the Company's annual goodwill impairment test in the fourth quarter of 2021 did not indicate an impairment. While no impairment was recognized during the year ended December 31, 2021, the Company anticipates that an impairment of the inflammation reporting unit's goodwill could occur in the next 12 to 18 months if the reporting unit does not achieve currently forecasted net sales and profitability estimates. These forecasts and estimates could be impacted by factors outside of the Company's control, such as increased competition from RAYOS generic entrants, which may result in an impairment.

Intangible Assets

As of December 31, 2021, the Company's finite-lived intangible assets consisted of developed technology related to ACTIMMUNE, BUPHENYL, KRYSTEXXA, PROCYSBI, RAVICTI, RAYOS, TEPEZZA and UPLIZNA as well as customer relationships for ACTIMMUNE. The intangible assets related to PENNSAID 2% and VIMOVO developed technology were fully amortized as of December 31, 2020.

In July 2021, in connection with the purchase of a biologic drug product manufacturing facility from EirGen, the Company capitalized \$21.8 million of intangible assets which are being amortized over a weighted-average estimated useful life of 16 years. Refer to Note 4 for further details.

On March 15, 2021, in connection with the acquisition of Viela, the Company capitalized \$1,460.0 million of developed technology related to UPLIZNA. Refer to Note 4 for further details.

In connection with the acquisition of River Vision, the Company capitalized payments of \$336.0 million related to TEPEZZA developed technology during the year ended December 31, 2020. Refer to Note 4 for further details on the River Vision acquisition.

Intangible assets as of December 31, 2021 and 2020 consisted of the following (in thousands):

	As of December 31,					
	2021			2020		
	Cost Basis	Accumulated Amortization	Net Book Value	Cost Basis	Accumulated Amortization	Net Book Value
Developed technology	\$ 4,579,171	\$ (1,642,427)	\$ 2,936,744	\$ 3,093,886	\$ (1,313,934)	\$ 1,779,952
In-process research and development (1)	880,000	—	880,000	—	—	—
Customer relationships and other intangibles	29,894	(6,520)	23,374	8,100	(5,090)	3,010
Total intangible assets	\$ 5,489,065	\$ (1,648,947)	\$ 3,840,118	\$ 3,101,986	\$ (1,319,024)	\$ 1,782,962

- (1) The Company acquired IPR&D of \$910.0 million relating to the Viela acquisition. On March 23, 2021, the Company's strategic partner, Mitsubishi Tanabe Pharma Corporation, received manufacturing and marketing approval of UPLIZNA in Japan. As a result, the Company transferred \$30.0 million of IPR&D to developed technology. As of December 31, 2021, the remaining IPR&D relating to the Viela acquisition was \$880.0 million.

Amortization expense for the years ended December 31, 2021, 2020 and 2019 was \$336.3 million, \$255.1 million and \$230.4 million, respectively. As of December 31, 2021, estimated future amortization expense was as follows (in thousands):

2022	\$	360,120
2023		353,121
2024		352,894
2025		352,311
2026		297,049
Thereafter		1,244,623
Total	\$	2,960,118

NOTE 9 – ACCRUED EXPENSES AND OTHER CURRENT LIABILITIES

Accrued expenses and other current liabilities as of December 31, 2021 and 2020 consisted of the following (in thousands):

	As of December 31,	
	2021	2020
Payroll-related expenses	\$ 147,439	\$ 121,577
Accrued royalties	108,215	68,006
R&D and manufacturing programs	54,076	17,289
Accrued upfront and milestone payments	35,100	123,442
Allowances for returns	33,881	40,918
Consulting and professional services	33,334	21,893
Pricing review liability	21,075	16,046
Advertising and marketing	16,930	12,428
Refund liability	16,711	—
Accrued interest	14,989	14,207
Accrued other	41,265	49,761
Accrued expenses and other current liabilities	\$ 523,015	\$ 485,567

NOTE 10 – ACCRUED TRADE DISCOUNTS AND REBATES

Accrued trade discounts and rebates as of December 31, 2021 and 2020 consisted of the following (in thousands):

	As of December 31,	
	2021	2020
Accrued government rebates and chargebacks	\$ 222,632	\$ 172,893
Accrued commercial rebates and wholesaler fees	48,761	82,646
Accrued co-pay and other patient assistance	46,038	96,924
Accrued trade discounts and rebates	\$ 317,431	\$ 352,463
Invoiced commercial rebates and wholesaler fees, co-pay and other patient assistance, and government rebates and chargebacks in accounts payable	—	1,452
Total customer-related accruals and allowances	\$ 317,431	\$ 353,915

The following table summarizes changes in the Company's customer-related accruals and allowances during the years ended December 31, 2021 and 2020 (in thousands):

	Government Rebates and Chargebacks	Commercial Rebates and Wholesaler Fees	Co-Pay and Other Patient Assistance	Total
Balance at December 31, 2019	\$ 164,508	\$ 138,761	\$ 163,641	\$ 466,910
Current provisions relating to sales during the year ended December 31, 2020	596,808	322,144	880,360	1,799,312
Adjustments relating to prior-year sales	(7,794)	(18,266)	(3,059)	(29,119)
Payments relating to sales during the year ended December 31, 2020	(424,401)	(240,122)	(783,517)	(1,448,040)
Payments relating to prior-year sales	(156,228)	(118,419)	(160,501)	(435,148)
Balance at December 31, 2020	\$ 172,893	\$ 84,098	\$ 96,924	\$ 353,915
Current provisions relating to sales during the year ended December 31, 2021	756,222	282,005	604,209	1,642,436
Adjustments relating to prior-year sales	(21,077)	(2,921)	(4,516)	(28,514)
Payments relating to sales during the year ended December 31, 2021	(538,086)	(233,314)	(558,182)	(1,329,582)
Payments relating to prior-year sales	(148,731)	(81,177)	(92,408)	(322,316)
Viela acquisition on March 15, 2021	1,411	70	11	1,492
Balance at December 31, 2021	\$ 222,632	\$ 48,761	\$ 46,038	\$ 317,431

NOTE 11 – SEGMENT AND OTHER INFORMATION

The Company has two reportable segments, the orphan segment and the inflammation segment, and the Company reports net sales and segment operating income for each segment.

On March 15, 2021, the Company completed its acquisition of Viela. The acquisition expanded the Company's commercial medicine portfolio by adding an additional rare disease medicine, UPLIZNA, to its orphan segment.

The orphan segment includes the medicines TEPEZZA, KRYSTEXXA, RAVICTI, PROCYSBI, ACTIMMUNE, UPLIZNA, BUPHENYL and QUINSAIR as well as the Company's R&D programs. The inflammation segment includes the medicines PENNSAID 2%, DUEXIS, RAYOS, VIMOVO and previously included MIGERGOT prior to the MIGERGOT transaction.

The Company's CODM evaluates the financial performance of the Company's segments based upon segment operating income. Segment operating income is defined as income (loss) before (benefit) expense for income taxes adjusted for the items set forth in the reconciliation below. Items below income from operations are not reported by segment, since they are excluded from the measure of segment profitability reviewed by the Company's CODM. Additionally, certain expenses are not allocated to a segment. The Company does not report balance sheet information by segment as no balance sheet by segment is reviewed by the Company's CODM.

The following table reflects net sales by medicine for the Company's reportable segments for the years ended December 31, 2021, 2020 and 2019 (in thousands):

	Year Ended December 31,		
	2021	2020	2019
TEPEZZA	\$ 1,661,299	\$ 820,008	\$ —
KRYSTEXXA	565,452	405,849	342,379
RAVICTI	291,945	261,615	228,755
PROCYSBI	189,965	170,102	161,941
ACTIMMUNE	117,164	118,834	107,302
UPLIZNA	60,805	—	—
BUPHENYL	7,860	10,549	9,806
QUINSAIR	1,028	698	817
Orphan segment net sales	\$ 2,895,518	\$ 1,787,655	\$ 851,000
PENNSAID 2%	191,621	178,011	200,756
DUEXIS	74,023	125,331	115,750
RAYOS	56,851	71,811	78,595
VIMOVO	8,397	37,621	52,106
MIGERGOT	—	—	1,822
Inflammation segment net sales	\$ 330,892	\$ 412,774	\$ 449,029
Total net sales	\$ 3,226,410	\$ 2,200,429	\$ 1,300,029

The table below provides reconciliations of the Company's segment operating income to the Company's total income (loss) before (benefit) expense for income taxes for the years ended December 31, 2021, 2020 and 2019 (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Segment operating income:			
Orphan	\$ 1,219,317	\$ 783,560	\$ 263,347
Inflammation	156,197	212,061	217,855
Reconciling items:			
Amortization and step-up:			
Intangible amortization expense	(336,277)	(255,148)	(230,424)
Inventory step-up expense	(27,572)	—	(89)
Share-based compensation	(219,086)	(146,627)	(91,215)
Acquisition/divestiture-related costs	(98,260)	(49,232)	(1,032)
Upfront and milestone payments related to license and collaboration agreements	(89,672)	(33,000)	(9,073)
Interest expense, net	(81,063)	(59,616)	(87,089)
Restructuring and realignment costs	(26,309)	141	(237)
Depreciation	(17,475)	(24,303)	(6,733)
Impairment of long-lived assets	(12,371)	(1,713)	—
Litigation settlements	(5,000)	—	(1,000)
Manufacturing plant start-up costs	(3,622)	—	—
Foreign exchange (loss) gain	(1,028)	(297)	33
Fees relating to refinancing activities	—	(54)	(2,292)
Loss on debt extinguishment	—	(31,856)	(58,835)
Drug substance harmonization costs	—	(542)	(457)
Charges relating to discontinuation of Friedreich's ataxia program	—	—	(1,076)
(Gain) loss on sale of assets	2,000	4,883	(10,963)
Gain on equity security investments	1,257	—	—
Other income (expense), net	1,791	3,388	(944)
Income (loss) before (benefit) expense for income taxes	\$ 462,827	\$ 401,645	\$ (20,224)

The following table presents the amount and percentage of gross sales to customers that represented more than 10% of the Company's gross sales included in its two reportable segments, and all other customers as a group for the years ended December 31, 2021, 2020 and 2019 (in thousands, except percentages):

	Year ended December 31,					
	2021		2020		2019	
	Amount	% of Gross Sales	Amount	% of Gross Sales	Amount	% of Gross Sales
Customer A	\$ 1,412,007	29%	\$ 1,298,128	32%	\$1,414,617	36%
Customer B	1,300,020	26%	959,066	24%	757,138	19%
Customer C	917,535	19%	772,724	19%	664,454	17%
Customer D	839,863	17%	521,425	13%	342,694	9%
Other Customers	434,204	9%	488,088	12%	732,921	19%
Gross Sales	\$ 4,903,629	100%	\$ 4,039,431	100%	\$3,911,824	100%

Geographic revenues are determined based on the country in which the Company's customers are located. The following table presents a summary of net sales attributed to geographic sources for the years ended December 31, 2021, 2020 and 2019 (in thousands, except percentages):

	Year Ended December 31, 2021		Year Ended December 31, 2020		Year Ended December 31, 2019	
	Amount	% of Total Net Sales	Amount	% of Total Net Sales	Amount	% of Total Net Sales
United States	\$ 3,210,020	100%	\$ 2,191,111	100%	\$ 1,292,419	100%
Rest of world	16,390	*	9,318	*	7,610	*
	<u>\$ 3,226,410</u>		<u>\$ 2,200,429</u>		<u>\$ 1,300,029</u>	

*Less than 1%

The following table presents total tangible long-lived assets by location as of the years ended December 31, 2021 and 2020 (in thousands):

	As of December 31,	
	2021	2020
United States	\$ 239,440	\$ 214,563
Ireland	128,498	8,726
Other	74	154
Total long-lived assets ⁽¹⁾	<u>\$ 368,012</u>	<u>\$ 223,443</u>

(1) Long-lived assets consist of property, plant and equipment and right-of-use lease assets.

NOTE 12 – FAIR VALUE MEASUREMENTS

The following tables and paragraphs set forth the Company's financial instruments that are measured at fair value on a recurring basis within the fair value hierarchy. Assets and liabilities measured at fair value are classified in their entirety based on the lowest level of input that is significant to the fair value measurement. The Company's assessment of the significance of a particular input to the fair value measurement in its entirety requires management to make judgments and consider factors specific to the asset or liability. The following describes three levels of inputs that may be used to measure fair value:

Level 1—Observable inputs such as quoted prices in active markets for identical assets or liabilities;

Level 2—Observable inputs other than Level 1 prices such as quoted prices for similar assets or liabilities, quoted prices in markets that are not active, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities; and

Level 3—Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

As of December 31, 2021, the Company's cash and cash equivalents included bank time deposits which were measured at fair value using Level 2 inputs and their carrying values were approximately equal to their fair values. Level 2 inputs, obtained from various third-party data providers, 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.

The Company utilizes the market approach to measure fair value for its money market funds. The market approach uses prices and other relevant information generated by market transactions involving identical or comparable assets or liabilities.

Other current assets and other long-term liabilities recorded at fair value on a recurring basis are composed of investments held in a rabbi trust and the related deferred liability for deferred compensation arrangements. Quoted prices for this investment, primarily in mutual funds, are available in active markets. Thus, the Company's investments related to deferred compensation arrangements and the related long-term liability are classified as Level 1 measurements in the fair value hierarchy.

Assets and liabilities measured at fair value on a recurring basis

The following tables set forth the Company's financial assets and liabilities at fair value on a recurring basis as of December 31, 2021 and 2020 (in thousands):

	December 31, 2021			Total
	Level 1	Level 2	Level 3	
Assets:				
Bank time deposits	\$ —	\$ 11,867	\$ —	\$ 11,867
Money market funds	1,367,500	—	—	1,367,500
Equity securities ⁽¹⁾	13,185	—	—	13,185
Other current assets	26,519	—	—	26,519
Total assets at fair value	\$ 1,407,204	\$ 11,867	\$ —	\$ 1,419,071
Liabilities:				
Other long-term liabilities	(26,519)	—	—	(26,519)
Total liabilities at fair value	\$ (26,519)	\$ —	\$ —	\$ (26,519)

- (1) The Company held investments in equity securities with readily determinable fair values of \$13.2 million as of December 31, 2021 which are included in other assets in the consolidated balance sheet. For the year ended December 31, 2021, the Company recognized net unrealized gains of \$1.3 million due to the change in fair value of these securities. There were no sales of equity securities for the year ended December 31, 2021.

	December 31, 2020			Total
	Level 1	Level 2	Level 3	
Assets:				
Money market funds	\$ 1,906,000	\$ —	\$ —	\$ 1,906,000
Other current assets	18,423	—	—	18,423
Total assets at fair value	\$ 1,924,423	\$ —	\$ —	\$ 1,924,423
Liabilities:				
Other long-term liabilities	(18,423)	—	—	(18,423)
Total liabilities at fair value	\$ (18,423)	\$ —	\$ —	\$ (18,423)

NOTE 13 – DEBT AGREEMENTS

The Company's outstanding debt balances as of December 31, 2021 and 2020 consisted of the following (in thousands):

	As of December 31,	
	2021	2020
Term Loan Facility due 2028	\$ 1,588,000	\$ —
Term Loan Facility due 2026	418,026	418,026
Senior Notes due 2027	600,000	600,000
Total face value	2,606,026	1,018,026
Debt discount	(12,164)	(10,061)
Deferred financing fees	(22,629)	(4,586)
Total long-term debt	2,571,233	1,003,379
Less: current maturities	16,000	—
Long-term debt, net of current maturities	\$ 2,555,233	\$ 1,003,379

Scheduled maturities with respect to the Company's long-term debt are as follows (in thousands):

2022	\$	(16,000)
2023		(16,000)
2024		(16,000)
2025		(16,000)
2026		(434,026)
Thereafter		(2,108,000)
Total	\$	(2,606,026)

Term Loan Facility and Revolving Credit Facility

On March 15, 2021, Horizon Therapeutics USA, Inc. (the "Borrower" or "HTUSA"), a wholly-owned subsidiary of the Company, borrowed approximately \$1.6 billion aggregate principal amount of loans (the "2028 Term Loans") pursuant to an amendment (the "March 2021 Amendment") to the credit agreement, dated as of May 7, 2015, by and among the Borrower, the Company and certain of its subsidiaries as guarantors, the lenders party thereto from time to time and Citibank, N.A., as administrative agent and collateral agent, as amended by Amendment No. 1, dated as of October 25, 2016, Amendment No. 2, dated March 29, 2017, Amendment No. 3, dated October 23, 2017, Amendment No. 4, dated October 19, 2018, Amendment No. 5, dated March 11, 2019, Amendment No. 6, dated May 22, 2019, Amendment No. 7, dated December 18, 2019 and the Incremental Amendment and Joinder Agreement, dated August 17, 2020 (the "Term Loan Facility"). Pursuant to Amendment No. 7, the Borrower borrowed approximately \$418.0 million aggregate principal amount of loans (the "2026 Term Loans"). Pursuant to Amendment No. 5, the Borrower received \$200.0 million aggregate principal amount of revolving commitments, which was increased to \$275.0 million aggregate amount of revolving commitments (the "Incremental Revolving Commitments") pursuant to the Incremental Amendment and Joinder Agreement. The Incremental Revolving Commitments were established pursuant to an incremental facility (the "Revolving Credit Facility") and includes a \$50.0 million letter of credit sub-facility. The Incremental Revolving Commitments will terminate in March 2024. Borrowings under the Revolving Credit Facility are available for general corporate purposes. As of December 31, 2021, the Revolving Credit Facility was undrawn. As used herein, all references to the "Credit Agreement" are references to the original credit agreement, dated as of May 7, 2015, as amended through the March 2021 Amendment.

The 2028 Term Loans were incurred as a separate class of term loans under the Credit Agreement with substantially the same terms of the 2026 Term Loans. The Borrower used the proceeds of the 2028 Term Loans to fund a portion of the consideration payable in the acquisition of Viela. The 2028 Term Loans bear interest at a rate, at Borrower's option, equal to the London Inter-Bank Offered Rate ("LIBOR"), plus 2.00% per annum (subject to a 0.50% LIBOR floor) or the adjusted base rate plus 1.00% per annum, with a step-down to LIBOR plus 1.75% per annum or the adjusted base rate plus 0.75% per annum at the time the Company's leverage ratio is less than or equal to 2.00 to 1.00. The adjusted base rate is defined as the greatest of (a) LIBOR (using one-month interest period) plus 1.00%, (b) the prime rate, (c) the federal funds rate plus 0.50%, and (d) 1.00%.

The 2026 Term Loans were incurred as a separate new class of term loans under the Credit Agreement with substantially the same terms as the previously outstanding senior secured term loans incurred on May 22, 2019 (the "Refinanced Loans") to effectuate a repricing of the Refinanced Loans. The Borrower used the proceeds of the 2026 Term Loans to repay the Refinanced Loans, which totaled approximately \$418.0 million. The 2026 Term Loans bear interest at a rate, at the Borrower's option, equal to LIBOR plus 2.25% per annum (subject to a 0.00% LIBOR floor) or the adjusted base rate plus 1.25% per annum, with a step-down to LIBOR plus 2.00% per annum or the adjusted base rate plus 1.00% per annum at the time the Company's leverage ratio is less than or equal to 2.00 to 1.00.

The loans under the Revolving Credit Facility bear interest, at the Borrower's option, at a rate equal to either LIBOR plus an applicable margin of 2.25% per annum (subject to a LIBOR floor of 0.00%), or the adjusted base rate plus 1.25% per annum, with a step-down to LIBOR plus 2.00% per annum or the adjusted base rate plus 1.00% per annum at the time the Company's leverage ratio is less than or equal to 2.00 to 1.00. The Credit Agreement provides for (i) the 2028 Term Loans, (ii) the 2026 Term Loans, (iii) the Revolving Credit Facility, (iv) one or more uncommitted additional incremental loan facilities subject to the satisfaction of certain financial and other conditions, and (v) one or more uncommitted refinancing loan facilities with respect to loans thereunder. The Credit Agreement allows for the Company and certain of its subsidiaries to become additional borrowers under incremental or refinancing facilities.

The obligations under the Credit Agreement (including obligations in respect of the 2028 Term Loans, 2026 Term Loans and the Revolving Credit Facility) and any swap obligations and cash management obligations owing to a lender (or an affiliate of a lender) are guaranteed by the Company and each of the Company's existing and subsequently acquired or formed direct and indirect subsidiaries (other than certain immaterial subsidiaries, subsidiaries whose guarantee would result in material adverse tax consequences and subsidiaries whose guarantee is prohibited by applicable law). The obligations under the Credit Agreement (including obligations in respect of the 2028 Term Loans, 2026 Term Loans and the Revolving Credit Facility) and any related swap and cash management obligations are secured, subject to customary permitted liens and other agreed upon exceptions, by a perfected security interest in (i) all tangible and intangible assets of the Borrower and the guarantors, except for certain customary excluded assets, and (ii) all of the capital stock owned by the Borrower and guarantors thereunder (limited, in the case of the stock of certain non-U.S. subsidiaries of the Borrower, to 65% of the capital stock of such subsidiaries). The Borrower and the guarantors under the Credit Agreement are individually and collectively referred to herein as a "Loan Party" and the "Loan Parties," as applicable.

The Borrower is permitted to make voluntary prepayments of the loans under the Credit Agreement at any time without payment of a premium. The Borrower is required to make mandatory prepayments of loans under the Credit Agreement (without payment of a premium) with (a) net cash proceeds from certain non-ordinary course asset sales (subject to reinvestment rights and other exceptions), (b) casualty proceeds and condemnation awards (subject to reinvestment rights and other exceptions), (c) net cash proceeds from issuances of debt (other than certain permitted debt), and (d) 50% of the Company's excess cash flow (subject to decrease to 25% or 0% if the Company's first lien leverage ratio is less than 2.25:1 or 1.75:1, respectively). The 2028 Term Loans will amortize in equal quarterly installments in an aggregate annual amount equal to 1% of the original principal amount thereof, with any remaining balance payable on March 15, 2028, the final maturity date of the 2028 Term Loans. The principal amount of the 2026 Term Loans is due and payable on May 22, 2026, the final maturity date of the 2026 Term Loans.

The Credit Agreement contains customary representations and warranties and customary affirmative and negative covenants, including, among other things, restrictions on indebtedness, liens, investments, mergers, dispositions, prepayment of other indebtedness and dividends and other distributions. The Credit Agreement also contains a springing financial maintenance covenant, which requires that the Company maintain a specified leverage ratio at the end of each fiscal quarter. The covenant is tested if both the outstanding loans and letters of credit under the Revolving Credit Facility, subject to certain exceptions, exceed 25% of the total commitments under the Revolving Credit Facility as of the last day of any fiscal quarter. If the Company fails to meet this covenant, the commitments under the Revolving Credit Facility could be terminated and any outstanding borrowings, together with accrued interest, under the Revolving Credit Facility could be declared immediately due and payable.

Other events of default under the Credit Agreement include: (i) the failure by the Borrower to timely make payments due under the Credit Agreement; (ii) material misrepresentations or misstatements in any representation or warranty by any Loan Party when made; (iii) failure by any Loan Party to comply with the covenants under the Credit Agreement and other related agreements; (iv) certain defaults under a specified amount of other indebtedness of the Company or its subsidiaries; (v) insolvency or bankruptcy-related events with respect to the Company or any of its material subsidiaries; (vi) certain undischarged judgments against the Company or any of its restricted subsidiaries; (vii) certain ERISA-related events reasonably expected to have a material adverse effect on the Company and its restricted subsidiaries taken as a whole; (viii) certain security interests or liens under the loan documents ceasing to be, or being asserted by the Company or its restricted subsidiaries not to be, in full force and effect; (ix) any loan document or material provision thereof ceasing to be, or any challenge or assertion by any Loan Party that such loan document or material provision is not, in full force and effect; and (x) the occurrence of a change of control. If one or more events of default occurs and continues beyond any applicable cure period, the administrative agent may, with the consent of the lenders holding a majority of the loans and commitments under the facilities, or will, at the request of such lenders, terminate the commitments of the lenders to make further loans and declare all of the obligations of the Loan Parties under the Credit Agreement to be immediately due and payable.

The interest on the 2028 Term Loans is variable and as of December 31, 2021, the interest rate on the 2028 Term Loans was 2.25% and the effective interest rate was 2.50%.

The interest on the 2026 Term Loans is variable and as of December 31, 2021, the interest rate on the 2026 Term Loans was 2.13% and the effective interest rate was 2.42%.

As of December 31, 2021, the fair value of the amounts outstanding under the 2028 Term Loans and the 2026 Term Loans was approximately \$1,580.1 million and \$415.9 million, respectively, categorized as a Level 2 instrument, as defined in Note 12.

2027 Senior Notes

On July 16, 2019, HTUSA completed a private placement of \$600.0 million aggregate principal amount of 5.5% Senior Notes due 2027 (the “2027 Senior Notes”) to several investment banks acting as initial purchasers, who subsequently resold the 2027 Senior Notes to persons reasonably believed to be qualified institutional buyers.

The Company used the net proceeds from the offering of the 2027 Senior Notes, together with approximately \$65.0 million in cash on hand, to redeem or prepay \$625.0 million of its outstanding debt, consisting of (i) the outstanding \$225.0 million principal amount of its 6.625% Senior Notes due 2023, (ii) the outstanding \$300.0 million principal amount of its 8.750% Senior Notes due 2024 and (iii) \$100.0 million of the outstanding principal amount of senior secured term loans under the Credit Agreement, as well as to pay the related premiums and fees and expenses, excluding accrued interest, associated with such redemption and prepayment.

The 2027 Senior Notes are HTUSA’s general unsecured senior obligations, rank equally in right of payment with all existing and future senior debt of HTUSA and rank senior in right of payment to any existing and future subordinated debt of HTUSA. The 2027 Senior Notes are effectively subordinate to all of the existing and future secured debt of HTUSA to the extent of the value of the collateral securing such debt.

The 2027 Senior Notes are unconditionally guaranteed on a senior basis by the Company and all of the Company’s restricted subsidiaries, other than HTUSA and certain immaterial subsidiaries, that guarantee the Credit Agreement. The guarantees are each guarantor’s senior unsecured obligations and rank equally in right of payment with such guarantor’s existing and future senior debt and senior in right of payment to any existing and future subordinated debt of such guarantor. The guarantees are effectively subordinated to all of the existing and future secured debt of each guarantor, including such guarantor’s guarantee under the Credit Agreement, to the extent of the value of the collateral securing such debt. The guarantees of a guarantor may be released under certain circumstances. The 2027 Senior Notes are structurally subordinated to all of the liabilities of the Company’s subsidiaries that do not guarantee the 2027 Senior Notes.

The 2027 Senior Notes accrue interest at an annual rate of 5.5% payable semiannually in arrears on February 1 and August 1 of each year, beginning on February 1, 2020. The 2027 Senior Notes will mature on August 1, 2027, unless earlier exchanged, repurchased or redeemed.

Except as described below, the 2027 Senior Notes may not be redeemed before August 1, 2022. Thereafter, some or all of the 2027 Senior Notes may be redeemed at any time at specified redemption prices, plus accrued and unpaid interest to the redemption date. At any time prior to August 1, 2022, some or all of the 2027 Senior Notes may be redeemed at a price equal to 100% of the aggregate principal amount thereof, plus a make-whole premium and accrued and unpaid interest to the redemption date. Also prior to August 1, 2022, up to 40% of the aggregate principal amount of the 2027 Senior Notes may be redeemed at a redemption price of 105.5% of the aggregate principal amount thereof, plus accrued and unpaid interest, with the net proceeds of certain equity offerings. In addition, the 2027 Senior Notes may be redeemed in whole but not in part at a redemption price equal to 100% of the principal amount plus accrued and unpaid interest and additional amounts, if any, to, but excluding, the redemption date, if on the next date on which any amount would be payable in respect of the 2027 Senior Notes, HTUSA or any guarantor is or would be required to pay additional amounts as a result of certain tax related events.

If the Company undergoes a change of control, HTUSA will be required to make an offer to purchase all of the 2027 Senior Notes at a price in cash equal to 101% of the aggregate principal amount thereof plus accrued and unpaid interest to, but not including, the repurchase date, subject to certain exceptions. If the Company or certain of its subsidiaries engages in certain asset sales, HTUSA will be required under certain circumstances to make an offer to purchase the 2027 Senior Notes at 100% of the principal amount thereof, plus accrued and unpaid interest to the repurchase date.

The indenture governing the 2027 Senior Notes contains covenants that limit the ability of the Company and its restricted subsidiaries to, among other things, pay dividends or distributions, repurchase equity, prepay junior debt and make certain investments, incur additional debt and issue certain preferred stock, incur liens on assets, engage in certain asset sales, merge, consolidate with or merge or sell all or substantially all of their assets, enter into transactions with affiliates, designate subsidiaries as unrestricted subsidiaries, and allow to exist certain restrictions on the ability of restricted subsidiaries to pay dividends or make other payments to the Company. Certain of the covenants will be suspended during any period in which the 2027 Senior Notes receive investment grade ratings. The indenture governing the 2027 Senior Notes also includes customary events of default.

As of December 31, 2021, the interest rate on the 2027 Senior Notes was 5.50% and the effective interest rate was 5.76%.

As of December 31, 2021, the fair value of the 2027 Senior Notes was approximately \$630.8 million, categorized as a Level 2 instrument, as defined in Note 12.

NOTE 14 – LEASE OBLIGATIONS

As of December 31, 2021, the Company had the following office space lease agreements in place for real properties:

Location	Approximate Square Feet	Lease Expiry Date
Dublin, Ireland (St. Stephen's Green) ⁽¹⁾	63,000	May 4, 2041
Lake Forest, Illinois	160,000	March 31, 2031
South San Francisco, California	20,000	January 31, 2030
Rockville, Maryland ⁽²⁾	24,500	August 31, 2023 to April 30, 2026
Chicago, Illinois	9,200	December 31, 2028
Gaithersburg, Maryland ⁽²⁾	7,200	June 30, 2022
Washington, D.C.	6,000	September 30, 2024
Mannheim, Germany	4,800	December 31, 2022

- (1) In October 2019, the Company entered into an agreement for lease relating to approximately 63,000 square feet of office space under construction on St. Stephen's Green in Dublin, Ireland. In May 2021, the construction of the office was completed by the lessor and the lease became effective. As a result, the Company recognized \$60.9 million as a right-of-use asset and a corresponding lease liability on the consolidated balance sheet. The lease is due to expire in May 2041. The Company incurred leasehold improvement costs during 2021 in order to prepare the building for occupancy. On November 1, 2021, the Company moved its Connaught House office employees to the St. Stephen's Green office. In July 2021, the Company entered into an agreement to assign the Connaught House lease to a third party and the lease assignment became effective on November 1, 2021.
- (2) On March 15, 2021, the Company completed its acquisition of Viela. As part of the acquisition, the Company assumed two leases in Rockville, Maryland for both office and laboratory space and a lease in Gaithersburg, Maryland for office space. On March 18, 2021, the Company entered into a third lease in Rockville, Maryland for office and laboratory space, with a lease commencement date of April 1, 2021.

The above table does not include details of an agreement to lease entered into in November 2021 relating to approximately 192,000 square feet of office and laboratory space under construction in Rockville, Maryland. Lease commencement will begin when construction of the building is completed by the lessor and the Company has access to begin the construction of leasehold improvements. The Company expects to receive access to the office and laboratory space and commence the related lease in the first half of 2023 and incur leasehold improvement costs through 2024 in order to prepare the building for occupancy. In addition, effective January 1, 2022, the South San Francisco, California office lease was amended to include an additional suite with approximately 20,000 square feet and the lease term on the existing lease was extended to December 31, 2031.

As of December 31, 2021 and 2020, the Company had right-of-use lease assets included in other assets of \$75.7 million and \$34.4 million, respectively; current lease liabilities included in accrued expenses and other current liabilities of \$3.6 million and \$4.1 million, respectively; and non-current lease liabilities included in other long-term liabilities of \$93.8 million and \$43.2 million, respectively, in its consolidated balance sheets.

In February 2021, the Company vacated the Lake Forest leased office building. As a result of the Company vacating the Lake Forest office, the Company recorded an impairment charge of \$12.4 million during the year ended December 31, 2021, using an income approach based on market prices for similar properties provided by a third-party. This charge was reported within impairment of long-lived asset in the consolidated statement of comprehensive income. In January 2022, the Company entered a sublease agreement for the entire Lake Forest office building for the remaining term of the original lease through March 31, 2031.

The Company recognizes rent expense on a monthly basis over the lease term based on a straight-line method. Rent expense was \$9.6 million and \$6.7 million for the years ended December 31, 2021 and 2020, respectively.

The table below reconciles the undiscounted cash flows for each of the first five years and total of the remaining years to the lease liabilities recorded on the Company's consolidated balance sheet as of December 31, 2021 (in thousands):

2022	\$	6,269
2023		9,986
2024		10,677
2025		10,414
2026		10,273
Thereafter		85,081
Total lease payments		132,700
Imputed interest		(35,299)
Total lease liabilities	\$	97,401

The weighted-average discount rate and remaining lease term for leases as of December 31, 2021 was 4.79% and 14.97 years, respectively.

NOTE 15 – COMMITMENTS AND CONTINGENCIES

Purchase Commitments

Under the Company's supply agreement with AGC Biologics A/S (formerly known as CMC Biologics A/S) ("AGC Biologics"), the Company has agreed to purchase certain minimum annual order quantities of TEPEZZA drug substance. In addition, the Company must provide AGC Biologics with rolling forecasts of TEPEZZA drug substance requirements, with a portion of the forecast being a firm and binding order. At December 31, 2021, the Company had binding purchase commitments with AGC Biologics for TEPEZZA drug substance of €122.8 million (\$139.2 million converted at a Euro-to-Dollar exchange rate as of December 31, 2021 of 1.1338), to be delivered through December 2024. Under the Company's supply agreement with Catalent Indiana, LLC ("Catalent"), the Company must provide Catalent with rolling forecasts of TEPEZZA drug product requirements, with a portion of the forecast being a firm and binding order. At December 31, 2021, the Company had binding purchase commitments with Catalent for TEPEZZA drug product of \$5.9 million, to be delivered through December 2022. The Company received FDA approval in December 2021 for a second drug product manufacturer, Patheon. Under the Company's supply agreement with Patheon, the Company must provide Patheon with rolling forecasts of TEPEZZA drug product requirements, with a portion of the forecast being a firm and binding order. As of December 31, 2021, the Company had binding purchase commitments with Patheon for TEPEZZA drug product of €3.4 million (\$3.9 million converted at an exchange rate as of December 31, 2021 of 1.1338), to be delivered through December 2022.

In December 2020, pursuant to the Defense Production Act of 1950 (“DPA”), Catalent was ordered to prioritize certain COVID-19 vaccine manufacturing, resulting in the cancellation of previously guaranteed and contracted TEPEZZA drug product manufacturing slots which were required to maintain TEPEZZA supply. To offset the reduced slots allowed by the DPA and Catalent, the Company accelerated plans to increase the production scale of TEPEZZA drug product. In March 2021, the FDA approved a prior approval supplement to the TEPEZZA biologics license application (which was previously approved in January 2020), giving the Company authorization to manufacture more TEPEZZA drug product in a batch resulting in an increased number of vials with each manufacturing slot. The Company commenced resupply of TEPEZZA to the market in April 2021.

Under the Company’s agreement with Bio-Technology General (Israel) Ltd (“BTG Israel”), the Company has agreed to purchase certain minimum annual order quantities and is obligated to purchase at least 80 percent of its annual worldwide bulk product requirements for KRYSTEXXA from BTG Israel. The term of the agreement runs until December 31, 2030, and will automatically renew for successive three-year periods unless earlier terminated by either party upon three years’ prior written notice. The agreement may be terminated earlier by either party in the event of a force majeure, liquidation, dissolution, bankruptcy or insolvency of the other party, uncured material breach by the other party or after January 1, 2024, upon three years’ prior written notice. Under the agreement, if the manufacture of the bulk product is moved out of Israel, the Company may be required to obtain the approval of the Israel Innovation Authority (formerly known as Israeli Office of the Chief Scientist) (“IIA”) because certain KRYSTEXXA intellectual property was initially developed with a grant funded by the IIA. The Company issues eighteen-month forecasts of the volume of KRYSTEXXA that the Company expects to order. The first nine months of the forecast are considered binding firm orders. At December 31, 2021, the Company had a total purchase commitment, including the minimum annual order quantities and binding firm orders, with BTG Israel for KRYSTEXXA of \$32.0 million, to be delivered through December 2026. Additionally, there were other purchase orders relating to the manufacture of KRYSTEXXA of \$1.0 million outstanding at December 31, 2021.

Under an agreement with Boehringer Ingelheim Biopharmaceuticals GmbH (“Boehringer Ingelheim Biopharmaceuticals”), Boehringer Ingelheim Biopharmaceuticals is required to manufacture and supply ACTIMMUNE to the Company. The Company is required to purchase minimum quantities of finished medicine during the term of the agreement, which term extends to at least September 30, 2024. As of December 31, 2021, the minimum purchase commitment to Boehringer Ingelheim Biopharmaceuticals was \$12.5 million (converted using a Euro-to-Dollar exchange rate of 1.1338 as of December 31, 2021) through September 2024.

Excluding the above, additional purchase orders and other commitments relating to the manufacture of BUPHENYL, DUEXIS, PROCYSBI, PENNSAID 2%, QUINSAIR, RAVICTI, RAYOS, TEPEZZA and UPLIZNA of \$15.9 million were outstanding at December 31, 2021.

Royalty and Milestone Agreements

TEPEZZA

River Vision Acquisition Agreement and S.R. One/Lundbeckfond Agreements

Under the acquisition agreement for River Vision in May 2017, the Company agreed to pay up to \$325.0 million upon the attainment of various milestones, composed of \$100.0 million related to FDA approval and \$225.0 million related to net sales thresholds for TEPEZZA.

The agreement also included a royalty payment of 3 percent of the portion of annual worldwide net sales exceeding \$300.0 million.

S.R. One and Lundbeckfond, as two of the former River Vision stockholders, both held rights to receive approximately 35.66% of any future TEPEZZA payments. As a result of the Company's agreements with S.R. One and Lundbeckfond in April 2020, the Company's remaining net obligations to make TEPEZZA payments for sales milestones and royalties to the former stockholders of River Vision was reduced by approximately 70.25%, after including payments to a third party. This resulted in milestone payments of \$67.0 million to the other former River Vision stockholders during the year ended December 31, 2021. There are no further TEPEZZA net sales milestone obligations remaining to the former River Vision stockholders. In addition, as a result of the S.R. One and Lundbeckfond agreements, annual earnout payments of 0.893 percent are due on the portion of annual worldwide net sales exceeding \$300.0 million.

Roche License Agreement

Under the Company's license agreement with Roche, the Company is required to pay Roche up to CHF103.0 million upon the attainment of various development, regulatory and sales milestones for TEPEZZA. The Company made a milestone payment of CHF5.0 million (\$5.2 million when converted using a CHF-to-Dollar exchange rate at the date of payment of 1.0382) related to FDA approval during the first quarter of 2020. The agreement with Roche also includes tiered royalties on annual worldwide net sales between 9 and 12 percent. During the year ended December 31, 2021, the Company made a milestone payment of CHF50.0 million (\$56.1 million when converted using a CHF-to-Dollar exchange rate at the date of payment of 1.1228) in relation to the attainment of TEPEZZA net sales milestones.

The Company's remaining obligation to Roche relating to the attainment of various TEPEZZA development and regulatory milestones is CHF43.0 million (\$47.0 million when converted using a CHF-to-Dollar exchange rate at December 31, 2021 of 1.0937).

KRYSTEXXA

Under the terms of a license agreement with Duke University ("Duke") and Mountain View Pharmaceuticals, Inc. ("MVP"), the Company is obligated to pay Duke a mid-single-digit royalty on its global net sales of KRYSTEXXA and a royalty of between 5% and 15% on any global sublicense revenue. The Company is also obligated to pay MVP a mid-single-digit royalty on its net sales of KRYSTEXXA outside of the United States and a royalty of between 5% and 15% on any sublicense revenue outside of the United States.

RAVICTI

Under the terms of an asset purchase agreement with Bausch Health Companies Inc. (formerly Ucycle Pharma, Inc.) ("Bausch"), the Company is obligated to pay to Bausch mid-single-digit royalties on its global net sales of RAVICTI. Under the terms of a license agreement with Saul W. Brusilow, M.D. and Brusilow Enterprises, Inc. ("Brusilow"), the Company is obligated to pay low single-digit royalties to Brusilow on net sales of RAVICTI that are covered by a valid claim of a licensed patent.

PROCYSBI

Under the terms of an amended and restated license agreement with The Regents of the University of California, San Diego ("UCSD"), as amended, the Company is obligated to pay to UCSD tiered low to mid-single-digit royalties on its net sales of PROCYSBI, including a minimum annual royalty in an amount less than \$0.1 million. The Company must also pay UCSD a percentage in the mid-teens of any fees it receives from its sublicensees under the agreement that are not earned royalties. The Company may also be obligated to pay UCSD aggregate developmental milestone payments of \$0.3 million and aggregate regulatory milestone payments of \$1.8 million for each orphan indication, and aggregate developmental milestone payments of \$0.8 million and aggregate regulatory milestone payments of \$3.5 million for each non-orphan indication.

ACTIMMUNE

Under an amended license agreement, with the original developer of ACTIMMUNE, the Company is obligated to pay a low single digit royalty on its annual net sales of ACTIMMUNE. In addition, under the terms of an assignment and option agreement with a separate third-party, the Company is obligated to pay low single-digit royalties on the Company's net sales of ACTIMMUNE in the United States.

UPLIZNA

Following the acquisition of Viela on March 15, 2021, the Company is party to a number of third-party license agreements. Under these license agreements, the Company is obligated to pay up to a total of \$30.0 million in milestone payments subject to UPLIZNA net sales exceeding \$500.0 million. In addition, the Company is required to pay mid-single-digit royalties on annual worldwide net sales of UPLIZNA.

RAYOS and LODOTRA

Effective January 1, 2019, the Company is obligated to pay Vectura a mid-teens percentage royalty on its RAYOS net sales in North America, subject to a minimum royalty of \$8.0 million per year, with the minimum royalty requirement expiring on December 31, 2022. In addition, under the amendments, the Company ceased recording LODOTRA revenue and is no longer required to pay a royalty in respect of LODOTRA.

For all of the royalty agreements entered into by the Company, a total royalty expense of \$277.5 million was recorded in cost of goods sold in the consolidated statements of comprehensive income during the year ended December 31, 2021. A total royalty expense of \$164.6 million was recorded in cost of goods sold in the consolidated statements of comprehensive income during the year ended December 31, 2020. A total royalty expense of \$71.5 million was recorded in cost of goods sold in the consolidated statements of comprehensive income during the year ended December 31, 2019.

Contingencies

The Company is subject to claims and assessments from time to time in the ordinary course of business. The Company's management does not believe that any such matters, individually or in the aggregate, will have a material adverse effect on the Company's business, financial condition, results of operations or cash flows. In addition, the Company from time to time has billing disputes with vendors in which amounts invoiced are not in accordance with the terms of their contracts.

Disclosure of ongoing matters is considered at the time of each filing and matters may be removed if the statute of limitations has lapsed or circumstances have changed that reduce the risk of exposure.

License Agreements

On December 15, 2021, the Company entered into an exclusive license agreement with Alpine for the development and commercialization of up to four preclinical candidates generated from Alpine's unique discovery platform. In connection with the execution of the license agreement, the Company entered into a stock purchase agreement with Alpine to purchase a minority stake of 951,980 shares of Alpine's common stock in a private placement.

Under the terms of the agreements, the Company paid Alpine \$15.0 million in the fourth quarter of 2021 and paid \$25.0 million in the first quarter of 2022. In addition, Alpine is eligible to receive up to \$381.0 million per program, or approximately \$1.52 billion in total, in future success-based payments related to development, regulatory and commercial milestones. Additionally, Alpine is eligible to receive tiered royalties from a mid-single digit percentage to a low double-digit percentage on global net sales. Alpine will advance candidate molecules to pre-defined preclinical milestones, and the Company will be responsible for the costs. The Company will then assume responsibility for development and commercialization activities and costs.

On June 18, 2021, the Company entered into a global agreement with Arrowhead for ARO-XDH, a previously undisclosed discovery-stage investigational RNAi therapeutic being developed by Arrowhead as a potential treatment for uncontrolled gout. Arrowhead granted the Company a worldwide exclusive license to develop, manufacture and commercialize products based on the RNAi therapeutic. Arrowhead will conduct all research and preclinical development activities for the RNAi therapeutic products. The Company must use commercially reasonable efforts in, and will be responsible for, clinical development and commercialization of the RNAi therapeutic products. Under the terms of the agreement, the Company paid Arrowhead an upfront cash payment of \$40.0 million in July 2021 and agreed to pay additional potential future milestone payments of up to \$660.0 million contingent on the achievement of certain development, regulatory and commercial milestones, and low to mid-teens royalties on worldwide calendar year net sales of licensed products.

On November 21, 2020, the Company entered into a global agreement with Halozyme that gives the Company exclusive access to Halozyme's ENHANZE drug delivery technology for SC formulation of medicines targeting IGF-1R. The Company is using ENHANZE to develop a SC formulation of TEPEZZA. Under the terms of the agreement, the Company paid Halozyme an upfront cash payment of \$30.0 million in December 2020 and agreed to pay additional potential future milestone payments of up to \$160.0 million contingent on the satisfaction of certain development and sales thresholds. The upfront payment was paid in December 2020.

Other Agreements

On April 1, 2020, the Company acquired Curzion for an upfront cash payment of \$45.0 million with additional payments of up to \$15.0 million contingent on the achievement of certain development and regulatory milestones. Under separate agreements with two additional parties, the Company is also required to make contingent payments upon the achievement of certain development and regulatory milestones and certain net sales thresholds. These separate agreements also include mid to high-single-digit royalty payments based on the portion of annual worldwide net sales.

During the year ended December 31, 2020, the Company committed to invest as a strategic limited partner in four venture capital funds: Forbion Growth Opportunities Fund I C.V., Forbion Capital Fund V C.V., Aisling Capital V, L.P. and RiverVest Venture Fund V, L.P. As of December 31, 2021, the total carrying amount of the Company's investments in these funds was \$22.6 million, which is included in other assets in the consolidated balance sheet, and includes \$12.7 million in net cash payments for investments made during the year ended December 31, 2021. As of December 31, 2021, the Company's total future commitments to these funds were \$42.3 million. During the years ended December 31, 2021 and 2020, the Company recorded investment income under the equity method of \$0.5 million and \$0.6 million, respectively, in the other income (expense), net line item of the Company's consolidated statement of comprehensive income related to these funds.

As of December 31, 2021, the Company had \$47.6 million of non-cancellable advertising commitments due within one year, primarily related to agreements for advertising for TEPEZZA and KRYSTEXXA.

Indemnification

In the normal course of business, the Company enters into contracts and agreements that contain a variety of representations and warranties and provide for general indemnifications. The Company's exposure under these agreements is unknown because it involves claims that may be made against the Company in the future, but have not yet been made. The Company may record charges in the future as a result of these indemnification obligations.

In accordance with its memorandum and articles of association, the Company has indemnification obligations to its officers and directors for certain events or occurrences, subject to certain limits, while they are serving at the Company's request in such capacity. Additionally, the Company has entered into, and intends to continue to enter into, separate indemnification agreements with its directors and executive officers. These agreements, among other things, require the Company to indemnify its directors and executive officers for certain expenses, including attorneys' fees, judgments, fines and settlement amounts incurred by a director or executive officer in any action or proceeding arising out of their services as one of the Company's directors or executive officers, or any of the Company's subsidiaries or any other company or enterprise to which the person provides services at the Company's request. The Company also has a director and officer insurance policy that enables it to recover a portion of any amounts paid for current and future potential claims.

NOTE 16 - LEGAL PROCEEDINGS

DUEXIS

On May 29, 2018, the Company received notice from Alkem Laboratories, Inc. (“Alkem”) that it had filed an Abbreviated New Drug Application (“ANDA”) with the FDA seeking approval of a generic version of DUEXIS. The ANDA contained a Paragraph IV Patent Certification alleging that the patents covering DUEXIS are invalid and/or will not be infringed by Alkem’s manufacture, use or sale of the medicine for which the ANDA was submitted. The Company filed suit in the United States District Court of Delaware against Alkem on July 9, 2018, seeking an injunction to prevent the approval of Alkem’s ANDA and/or to prevent Alkem from selling a generic version of DUEXIS. The litigation went to trial on September 14, 2020. On November 30, 2020, the District Court issued an adverse judgment against the Company, invalidating U.S. Patent No. 8,607,033 and finding that Alkem’s generic product would not infringe the ‘033 patent. Following an adverse claim construction ruling, the District Court entered a judgment that the Alkem generic product would not infringe U.S. Patent No. 8,607,451, subject to the Company’s right to appeal the District Court’s claim construction ruling. On December 23, 2020, the Company initiated an appeal of the adverse judgments on the ‘033 and ‘451 patents with the Federal Circuit Court of Appeals. On November 16, 2021, the Federal Circuit Court of Appeals affirmed the District Court’s judgment for Alkem, invalidating the ‘033 patent and finding the ‘451 patent not infringed.

On August 3, 2021, the FDA granted final approval for Alkem’s generic version of DUEXIS. On August 4, 2021, Alkem launched its generic version of DUEXIS in the United States, and the Company now faces generic competition with respect to DUEXIS.

On September 26, 2018, the Company received notice from Teva Pharmaceuticals USA, Inc. (“Teva USA”) that it had filed an ANDA with the FDA seeking approval of a generic version of DUEXIS. The ANDA contained a Paragraph IV Patent Certification alleging that the patents covering DUEXIS are invalid and/or will not be infringed by Teva USA’s manufacture, use or sale of the medicine for which the ANDA was submitted. The Company filed suit in the United States District Court of New Jersey against Teva USA on July 2, 2020, seeking to prevent Teva USA from selling a generic version of DUEXIS.

On May 24, 2021, the Company received notice from Torrent Pharmaceuticals Limited (“Torrent”) that it had filed an ANDA with the FDA seeking approval of a generic version of DUEXIS. The ANDA contained a Paragraph IV Patent Certification alleging that the patents covering DUEXIS are invalid and/or will not be infringed by Torrent’s manufacture, use or sale of the medicine for which the ANDA was submitted. The Company filed suit in the United States District Court of New Jersey against Torrent on July 7, 2021, seeking to prevent Torrent from selling a generic version of DUEXIS.

Following the Federal Circuit Court of Appeals’ affirmance in the Alkem appeal on November 16, 2021, the Company dismissed with prejudice the pending patent litigation against Teva USA and Torrent, which will allow each to seek approval and market a generic version of DUEXIS if they choose to do so.

VIMOVO

On February 18, 2020, the FDA granted final approval for Dr. Reddy’s Laboratories Inc. and Dr. Reddy’s Laboratories Ltd. (collectively, “Dr. Reddy’s”) generic version of VIMOVO. On February 27, 2020, Dr. Reddy’s launched its generic version of VIMOVO in the United States, and the Company now faces generic competition with respect to VIMOVO. The Company continues to assert claims of infringement against Dr. Reddy’s based on U.S. Patent No. 8,858,996 and U.S. Patent No. 9,161,920 in the District Court for the District of New Jersey. On February 25, 2022, the District Court granted Dr. Reddy’s request for summary judgment invalidating the ‘996 and ‘920 patents. The Company intends to appeal the District Court’s ruling to the Federal Circuit Court of Appeals.

PROCYSBI

On June 27, 2020, the Company received notice from Lupin Limited (“Lupin”) that it had filed an ANDA with the FDA seeking approval of a generic version of PROCYSBI. The ANDA contained a Paragraph IV Patent Certification alleging that the patents covering PROCYSBI are invalid and/or will not be infringed by Lupin’s manufacture, use or sale of the medicine for which the ANDA was submitted. The Company filed suit in the United States District Court of New Jersey against Lupin on August 11, 2020, seeking to prevent Lupin from selling a generic version of PROCYSBI. On September 30, 2021, the Company entered into a settlement agreement with Lupin resolving both the PROCYSBI patent litigation with respect to PROCYSBI capsules and potential future patent litigation involving PROCYSBI granules. Under the Company’s settlement agreement with Lupin, Lupin may enter the market on March 31, 2030, or earlier under certain circumstances.

On February 2, 2022 and February 16, 2022, the Company received notice from Teva Pharmaceuticals, Inc. (“Teva”) that it had filed ANDAs with the FDA seeking approval of generic versions of PROCYSBI granules and capsules, respectively. The ANDAs contained Paragraph IV Patent Certifications alleging that the patents covering PROCYSBI granules and capsules are invalid and/or will not be infringed by Teva’s manufacture, use or sale of the medicines for which the ANDAs were submitted. The Company intends to file suit against Teva for patent infringement, seeking to prevent Teva from selling generic versions of PROCYSBI granules and capsules.

NOTE 17 – SHAREHOLDERS’ EQUITY

During the year ended December 31, 2021, the Company issued an aggregate of 6.0 million ordinary shares in connection with stock option exercises, the vesting of restricted stock units and performance stock units and employee share purchase plan purchases. The Company received a total of \$73.1 million in net proceeds in connection with such issuances.

During the year ended December 31, 2021, the Company made payments of \$166.0 million for employee withholding taxes relating to share-based awards.

During the year ended December 31, 2020, the Company issued 13.6 million ordinary shares in connection with the closing of its underwritten public equity offering on August 11, 2020. The Company received net proceeds of approximately \$919.8 million after deducting underwriting discounts and other offering expenses payable by the Company in connection with such offering.

During the year ended December 31, 2020, the Company issued an aggregate of 5.9 million ordinary shares in connection with stock option exercises, the vesting of restricted stock units and performance stock units, and employee share purchase plan purchases. The Company received a total of \$53.0 million in net proceeds in connection with such issuances.

During the year ended December 31, 2020, the Company made payments of \$66.5 million for employee withholding taxes relating to share-based awards.

NOTE 18 – SHARE-BASED AND LONG-TERM INCENTIVE PLANS

Employee Share Purchase Plan

2020 Employee Share Purchase Plan. On February 19, 2020, the compensation committee of the Company’s board of directors (the “Compensation Committee”) adopted, subject to shareholder approval, the 2020 Employee Share Purchase Plan (“2020 ESPP”), as successor to and continuation of the 2014 Employee Share Purchase Plan (the “2014 ESPP”), including increasing the number of ordinary shares available for issuance to the Company’s employees pursuant to the exercise of purchase rights under our purchase plans by an additional 2,500,000 ordinary shares. On April 30, 2020, the shareholders of the Company approved the 2020 ESPP.

As of December 31, 2021, an aggregate of 2,375,485 ordinary shares were authorized and available for future issuance under the 2020 ESPP. The 2014 ESPP terminated following its final purchase date in June 2021. Any unpurchased shares that remained subject to the share reserve of the 2014 ESPP following its final purchase date were added to the 2,500,000 ordinary shares initially approved for the 2020 ESPP’s share reserve and are available for future issuance pursuant to purchase rights granted under the 2020 ESPP.

Share-Based Compensation Plans

2011 Equity Incentive Plan. Upon the effectiveness of the Horizon Therapeutics Public Limited Company Amended and Restated 2014 Equity Incentive Plan (the “2014 EIP”), no additional stock awards were or will be made under the 2011 Equity Incentive Plan (the “2011 EIP”), although all outstanding stock awards granted under the 2011 EIP continue to be governed by the terms of the 2011 EIP.

Amended and Restated 2014 Equity Incentive Plan and 2014 Non-Employee Equity Plan. On May 17, 2014, HPI’s board of directors adopted the 2014 EIP and the Horizon Therapeutics Public Limited Company 2014 Non-Employee Equity Plan (the “2014 Non-Employee Equity Plan”). At the Special Meeting, HPI’s stockholders approved the 2014 EIP and 2014 Non-Employee Equity Plan, which serve as successors to the 2011 EIP.

The 2014 EIP provides for the grant of incentive and nonstatutory stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards, performance awards and other stock awards that may be settled in cash, shares or other property to the employees of the Company (or a subsidiary company). During the year ended December 31, 2017, the Compensation Committee approved an amendment to the 2014 EIP to reserve additional shares to be used exclusively for grants of awards to individuals who were not previously employees or non-employee directors of the Company (or following a bona fide period of non-employment with the Company) (the “2017 Inducement Pool”), as an inducement material to the individual’s entry into employment with the Company within the meaning of Rule 5635(c)(4) of the Nasdaq Listing Rules, (“Rule 5635(c)(4)”). The 2014 EIP was amended by the Compensation Committee without shareholder approval pursuant to Rule 5635(c)(4). An amendment to the 2014 EIP increasing the number of ordinary shares that may be issued under the 2014 EIP by 10,800,000 ordinary shares was approved by the Compensation Committee on February 21, 2018 and by the shareholders of the Company on May 3, 2018.

The 2014 Non-Employee Equity Plan provides for the grant of non-statutory stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards and other forms of stock awards that may be settled in cash, shares or other property to the non-employee directors and consultants of the Company (or a subsidiary company). The Company’s board of directors has authority to suspend or terminate the 2014 Non-Employee Equity Plan at any time.

On February 20, 2019, the Compensation Committee approved, subject to shareholder approval, an amendment to the 2014 Non-Employee Equity Plan, increasing the number of ordinary shares that may be issued under the 2014 Non-Employee Equity Plan by 750,000 ordinary shares, subject to adjustment for certain changes in our capitalization. On May 2, 2019, the shareholders of the Company approved such amendment to the 2014 Non-Employee Equity Plan.

Amended and Restated 2020 Equity Incentive Plan. On February 19, 2020, the Compensation Committee adopted, subject to shareholder approval, the Amended and Restated 2020 Equity Incentive Plan (“2020 EIP”), as successor to and continuation of the 2014 EIP, including increasing the number of ordinary shares available for the grant of equity awards to the Company’s employees by an additional 6,900,000 shares. On April 30, 2020, the shareholders of the Company approved the 2020 EIP.

On February 17, 2021, the Compensation Committee approved amending the 2020 EIP, subject to shareholder approval, including increasing the number of ordinary shares available for the grant of equity awards to the Company’s employees by an additional 7,000,000 shares. On April 29, 2021, the shareholders of the Company approved such amendment to the 2020 EIP.

Amended and Restated 2018 Equity Incentive Plan. In connection with the Viela acquisition on March 15, 2021, the Company assumed the Viela Bio Amended and Restated 2018 Equity Incentive Plan (“Viela 2018 EIP”). The Viela 2018 EIP was subsequently renamed the Horizon Therapeutics Public Limited Company Amended and Restated 2018 Equity Incentive Plan (“2018 EIP”) on April 28, 2021. The maximum aggregate number of ordinary shares that may be issued under the 2018 EIP following March 15, 2021 (the “Plan Assumption Date”) is 3,677,603 ordinary shares, which is the sum of the 1,318,053 ordinary shares subject to outstanding awards assumed by the Company on the Plan Assumption Date, and the 2,359,550 ordinary shares available for grant under the plan’s unused reserve as of the Plan Assumption Date.

As of December 31, 2021, an aggregate of 16,199,091 ordinary shares were authorized and available for future grants under the 2020 EIP, an aggregate of 526,895 ordinary shares were authorized and available for future grants under the 2014 Non-Employee Equity Plan and an aggregate of 2,178,298 ordinary shares were authorized and available for future grants under the 2018 EIP.

Stock Options

There were no stock option grants in 2021 and 2020; however, the Company assumed 1.3 million outstanding employee and director stock options as a result of the Viela acquisition on March 15, 2021. The estimated fair value of the converted stock options was determined using a Hull-White model in a binomial lattice option pricing framework with the following weighted average assumptions:

Stock price (closing stock price on March 14, 2021)	\$	91.78
Weighted average fair value of converted stock options		\$26.05 to \$87.84
Risk-free interest rate		0.04% to 1.62%
Expected stock price volatility		50.06 % to 65.18%
Dividend yield		—
Term to expiration		0.25 years to 9.75 years

The following table summarizes stock option activity during the year ended December 31, 2021:

	Options	Weighted Average Exercise Price	Contractual Term Remaining (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2020	7,129,615	\$ 21.24	4.60	\$ 370,073
Assumed in acquisition ⁽¹⁾	1,318,053	41.23	—	—
Exercised	(2,114,749)	24.23	—	—
Forfeited	(119,961)	49.07	—	—
Expired	(3,375)	55.26	—	—
Outstanding as of December 31, 2021	6,209,583	23.91	3.95	520,651
Exercisable as of December 31, 2021	5,806,653	\$ 22.50	3.68	\$ 495,104

- (1) On March 15, 2021, the Company completed its acquisition of Viela. Under the terms of the merger agreement for Viela, all outstanding Viela stock options assumed by the Company with vesting dates after June 1, 2021, were converted into stock options to purchase the Company's ordinary shares. As of March 15, 2021, options previously exercisable for an aggregate of 2,180,159 shares of Viela's common stock that were converted at a rate of 0.60 to 1 based on the merger agreement, into options to purchase 1,318,053 of the Company's ordinary shares, were outstanding.

Stock options typically have a contractual term of ten years from grant date.

The following table summarizes the Company's outstanding stock options at December 31, 2021:

Exercise Price Ranges	Options Outstanding			Options Exercisable		
	Number of options outstanding	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in years)	Number Exercisable	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in years)
\$2.01 - \$4.00	17,988	\$ 2.82	1.25	17,988	\$ 2.82	1.25
\$4.01 - \$8.00	84,053	4.81	6.14	50,469	4.88	5.98
\$8.01 - \$12.00	72,686	8.73	3.20	62,577	8.74	2.55
\$12.01 - \$17.00	948,387	14.40	4.72	904,872	14.35	4.58
\$17.01 - \$22.00	711,842	18.02	4.38	711,842	18.02	4.38
\$22.01 - \$28.00	2,309,580	22.35	3.37	2,243,473	22.24	3.25
\$28.01 - \$36.00	1,782,683	28.67	3.41	1,759,432	28.66	3.35
\$42.01 - \$81.00	282,364	64.38	8.07	56,000	65.03	7.89
	6,209,583	\$ 23.91	3.95	5,806,653	\$ 22.50	3.68

During the years ended December 31, 2021 and 2020, the Company did not grant any stock options, other than the Viela stock options assumed by the Company. During the year ended December 31, 2019, the Company granted stock options to purchase an aggregate of 69,752 ordinary shares, with a weighted average grant date fair value of \$15.77.

The total intrinsic value of the options exercised during the years ended December 31, 2021, 2020 and 2019 was \$160.1 million, \$79.8 million and \$28.2 million, respectively. The total fair value of stock options vested during the years ended December 31, 2021, 2020 and 2019 was \$51.4 million, \$3.5 million and \$13.8 million, respectively.

The fair value of each stock option award is estimated on the date of grant using the Black-Scholes option pricing model. The determination of the fair value of each stock option is affected by the Company's share price on the date of grant, as well as assumptions regarding a number of highly complex and subjective variables. These variables include, but are not limited to, the Company's expected share price volatility over the expected term of the awards and actual and projected stock option exercise behavior. The weighted average fair value per share of stock option awards granted during the year ended December 31, 2019, and assumptions used to value stock options, are as follows:

	2019
Dividend yield	—
Risk-free interest rate	1.6%
Weighted average volatility	56.5%
Expected term (in years)	6.00
Weighted average grant date fair value per share of options granted	\$ 15.77

Dividend yields

The Company has never paid dividends and does not anticipate paying any dividends in the near future. Additionally, the Credit Agreement (described in Note 13 above), as well as the indentures governing the 2027 Senior Notes (described in Note 13 above), contain covenants that restrict the Company from issuing dividends.

Risk-Free Interest Rate

The Company determined the risk-free interest rate by using a weighted average assumption equivalent to the expected term based on the U.S. Treasury constant maturity rate as of the date of grant.

Volatility

The Company used an average historical share price volatility of comparable companies to be representative of future share price volatility, as the Company did not have sufficient trading history for its ordinary shares.

Expected Term

Given the Company's limited historical exercise behavior, the expected term of options granted was determined using the "simplified" method since the Company did not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term. Under this approach, the expected term was presumed to be the average of the vesting term and the contractual life of the option.

Forfeitures

As share-based compensation expense recognized in the consolidated statements of comprehensive income is based on awards ultimately expected to vest, it has been reduced for estimated forfeitures based on actual forfeiture experience, analysis of employee turnover and other factors.

Restricted Stock Units

The following table summarizes restricted stock unit activity for the year ended December 31, 2021:

	Number of Units	Weighted Average Grant-Date Fair Value Per Unit
Outstanding as of December 31, 2020	5,909,120	\$ 27.87
Granted	2,211,264	78.35
Vested	(3,274,103)	24.32
Forfeited	(433,600)	59.74
Outstanding as of December 31, 2021	4,412,681	\$ 52.67

The grant-date fair value of restricted stock units is the closing price of the Company's ordinary shares on the date of grant.

During the years ended December 31, 2021, 2020 and 2019, the Company granted 2,211,264, 2,781,080 and 3,581,848 restricted stock units to acquire the Company's ordinary shares to its employees and non-executive directors, respectively, with a weighted average grant date fair value of \$78.35, \$39.01 and \$21.69, respectively. The restricted stock units vest annually, with a vesting period ranging from two to four years. The Company accounts for the restricted stock units as equity-settled awards in accordance with ASU No. 2017-09. The total fair value of restricted stock units vested during the years ended December 31, 2021, 2020 and 2019 was \$79.6 million, \$54.6 million and \$76.4 million, respectively.

Performance Stock Unit Awards

The following table summarizes performance stock unit awards ("PSUs") activity for the year ended December 31, 2021:

	Number of Units	Weighted Average Grant-Date Fair Value Per Unit	Average Illiquidity Discount	Recorded Weighted Average Fair Value Per Unit
Outstanding as of December 31, 2020	2,610,924			
Granted	450,577	\$ 93.73	8.64%	\$ 85.64
Forfeited	(24,450)	93.73	9.21%	85.10
Vested	(2,131,964)	23.18	3.44%	22.39
Performance Based Adjustment (1)	623,129	31.41	7.69%	29.00
Outstanding as of December 31, 2021	1,528,216			

- (1) Represents adjustment based on the net sales performance criteria meeting 162.5% of target as of December 31, 2020 for the 2020 PSUs (as defined below), the net sales performance criteria meeting 200.0% of target as of December 31, 2020 for the TEPEZZA PSUs (as defined below) and meeting total shareholder return ("TSR") performance at 200.0% for the PSUs that were awarded to key executive participants on January 5, 2018.

On January 4, 2021, the Company awarded PSUs to key executive participants ("2021 PSUs"). The 2021 PSUs utilize three long-term performance metrics: a component tied to relative TSR over a three-year period, a component tied to technical operations and manufacturing milestones for the Company over a three-year period, and a component tied to R&D and business development milestones for the Company over a two-year period, as follows:

- 50% of the 2021 PSUs that may vest (such portion of the PSU award, the "2021 Relative TSR PSUs") are determined by reference to the Company's TSR over the three-year period ending December 31, 2023, as measured relative to the TSR of each company included in the Nasdaq Biotechnology Index ("NBI") during such three-year period. Generally, in order to vest in any portion of the 2021 Relative TSR PSUs, the participant must also remain in continuous service with the Company through the earlier of January 5, 2024 or the date immediately prior to a change in control. If a change in control occurs prior to December 31, 2023, a portion of the 2021 Relative TSR PSUs will vest upon the change in control based on the level of the Company's relative TSR, as measured through the date of the change in control.

- 25% of the 2021 PSUs that may vest (such portion of the PSU award, the “2021 Tech Ops PSUs”) are determined by reference to the Company’s achievement of certain performance objectives related to technical operations and manufacturing during the three-year period ending December 31, 2023. Generally, in order to vest in any portion of the 2021 Tech Ops PSUs, the participant must also remain in continuous service with the Company through the earlier of January 5, 2024 or the date immediately prior to a change in control. If a change in control occurs prior to December 31, 2023, a portion of the 2021 Tech Ops PSUs will vest upon the change in control, with such portion calculated by reference to the greater of (i) the portion of the participant’s target PSU award applicable to the participant’s 2021 Tech Ops PSUs or (ii) such portion of the participant’s 2021 Tech Ops PSUs as would have been earned based on actual performance during the three-year period ending December 31, 2023 if the change in control had not occurred, to the extent reasonably calculable, and as determined by the Compensation Committee.
- 25% of the 2021 PSUs that may vest (such portion of the PSU award, the “2021 R&D PSUs”) are determined by reference to the Company’s achievement of certain performance objectives related to R&D and business development during the two-year period ending December 31, 2022. Generally, in order to vest in any portion of the 2021 R&D PSUs, the participant must also remain in continuous service with the Company through the earlier of (i) January 5, 2023 (with respect to 2/3rds of the 2021 R&D PSUs) and January 5, 2024 (with respect to 1/3rd of the 2021 R&D PSUs) or (ii) the date immediately prior to a change in control. If a change in control occurs prior to December 31, 2022, a portion of the 2021 R&D PSUs will vest upon the change in control, with such portion calculated by reference to the greater of (i) the portion of the participant’s target PSU award applicable to the participant’s 2021 R&D PSUs or (ii) such portion of the participant’s 2021 R&D PSUs as would have been earned based on actual performance during the two-year period ending December 31, 2022 if the change in control had not occurred, to the extent reasonably calculable, and as determined by the Compensation Committee.

During the year ended December 31, 2021, the Company’s board of directors approved the modification of certain outstanding awards of two senior executives that retired in January 2022. The modification terms contain a clause of continued vesting of performance awards post retirement that were originally scheduled to forfeit upon termination. This change in terms triggered a modification that resulted in an incremental expense of \$6.4 million accrued through the termination date.

On January 3, 2020, the Company awarded PSUs to key executive participants (“2020 PSUs”). The 2020 PSUs utilize two performance metrics: a component tied to relative TSR over a three-year period and a component tied to certain business performance milestones for the Company over one-year and two-year periods, as follows:

- 30% of the 2020 PSUs that may vest (such portion of the PSU award, the “2020 Relative TSR PSUs”) are determined by reference to the Company’s TSR over the three-year period ending December 31, 2022, as measured relative to the TSR of each company included in the NBI during such three-year period. Generally, in order to vest in any portion of the 2020 Relative TSR PSUs, the participant must also remain in continuous service with the Company through the earlier of January 1, 2023 or the date immediately prior to a change in control. If a change in control occurs prior to December 31, 2022, a portion of the 2020 Relative TSR PSUs will vest upon the change in control based on the level of the Company’s relative TSR, as measured through the date of the change in control.
- 70% of the 2020 PSUs that may vest (such portion of the PSU award, the “2020 Net Sales PSUs”) are determined by reference to the Company’s net sales for certain components of its orphan segment during the one-year period that ended on December 31, 2020 or the two-year period that ended on December 31, 2021, as applicable. Generally, in order to vest in any portion of the 2020 Net Sales PSUs, the participant must also remain in continuous service with the Company through certain dates (each of which occur following the end of the applicable performance period).

As a result of the impact of the COVID-19 pandemic on certain aspects of the Company's business in 2020, the performance goals associated with certain of the Company's performance-based equity awards no longer reflected the Company's expectations, causing the awards to lose their incentive to employees. Accordingly, on July 28, 2020, the Compensation Committee approved a modification to the 2020 Net Sales PSUs awarded on January 3, 2020 that were to vest based on KRYSTEXXA 2020 net sales. Those 2020 Net Sales PSUs related to KRYSTEXXA may now be earned based on net sales of KRYSTEXXA achieved by the end of a modified 18-month performance period that ended on June 30, 2021 instead of a 12-month performance period that ended on December 31, 2020. As a result, with respect to the 2020 Net Sales PSUs that were earned based on net sales of KRYSTEXXA, the first one-third vested on July 1, 2021, the second one-third vested on January 5, 2022 and the vesting of the remaining one-third is unchanged and will vest on January 5, 2023. There were 12 participants impacted by the modification. The total compensation cost resulting from the modification was approximately \$17.9 million and is being recognized over the remaining requisite service period.

All PSUs outstanding at December 31, 2021 may vest in a range of between 0% and 200%, with the exception of the modified KRYSTEXXA 2020 Net Sales PSUs which are capped at 150%, based on the performance metrics described above. The Company accounts for the 2020 PSUs and 2021 PSUs as equity-settled awards in accordance with ASC 718, *Compensation-Stock Compensation*. Because the value of the 2020 Relative TSR PSUs and 2021 Relative TSR PSUs are dependent upon the attainment of a level of TSR, it requires the impact of the market condition to be considered when estimating the fair value of the 2020 Relative TSR PSUs and 2021 Relative TSR PSUs. As a result, the Monte Carlo model is applied and the most significant valuation assumptions used related to the 2021 PSUs during the year ended December 31, 2021, include:

Valuation date stock price	\$	72.54
Expected volatility		45.8%
Risk free rate		0.2%

The value of the 2021 Tech Ops PSUs and 2021 R&D PSUs is calculated at the end of each quarter based on the expected payout percentage based on estimated full-period performance against targets, and the Company adjusts the expense quarterly.

On January 4, 2019, the Company awarded a company-wide grant of PSUs (the "TEPEZZA PSUs"). Vesting of the TEPEZZA PSUs was contingent upon receiving shareholder approval of amendments to the 2014 EIP, which approval was received on May 2, 2019. The TEPEZZA PSUs were generally eligible to vest contingent upon receiving approval of the TEPEZZA biologics license application from the FDA no later than September 30, 2020 and the employee's continued service with the Company. In January 2020, the Company received TEPEZZA approval from the FDA and the Company started recognizing the expense related to the TEPEZZA PSUs on that date. As of December 31, 2021, there were 68,459 TEPEZZA PSUs outstanding, for members of the executive committee, which subsequently vested on January 21, 2022. For all other participants, one-half of the TEPEZZA PSUs vested on the FDA approval date and one-half vested on the one-year anniversary of the FDA approval date, subject to the employee's continued service through the applicable vesting date.

Share-Based Compensation Expense

The following table summarizes share-based compensation expense included in the Company's consolidated statements of operations for the years ended December 31, 2021, 2020 and 2019 (in thousands):

	For the Years Ended December 31,		
	2021	2020	2019
Cost of goods sold	\$ 8,699	\$ 7,203	\$ 3,818
Research and development	39,544	13,973	9,117
Selling, general and administrative	170,843	125,451	78,280
Total share-based compensation expense	\$ 219,086	\$ 146,627	\$ 91,215

During the years ended December 31, 2021 and 2020, the Company recognized \$86.9 million and \$29.3 million of a tax benefit, respectively, related to share-based compensation resulting primarily from the fair value of equity awards in effect at the time of the exercise of stock options and vesting of restricted stock units and PSUs. As of December 31, 2021, the Company estimates that pre-tax unrecognized compensation expense of \$198.8 million for all unvested share-based awards, including stock options, restricted stock units and PSUs, will be recognized through the second quarter of 2023. The Company expects to satisfy the exercise of stock options and future distribution of shares for restricted stock units and PSUs by issuing new ordinary shares which have been reserved under the 2020 EIP and the 2018 EIP.

NOTE 19 – INCOME TAXES

The Company's income (loss) before (benefit) expense for income taxes by jurisdiction for the years ended December 31, 2021, 2020 and 2019 is as follows (in thousands):

	For the Years Ended December 31,		
	2021	2020	2019
Ireland	\$ 177,063	\$ 94,527	\$ 77,272
United States	35,711	(13,716)	(21,269)
Other foreign	250,053	320,834	(76,227)
Income (loss) before (benefit) expense for income taxes	\$ 462,827	\$ 401,645	\$ (20,224)

The components of the (benefit) expense for income taxes were as follows for the years ended December 31, 2021, 2020 and 2019 (in thousands):

	For the Years Ended December 31,		
	2021	2020	2019
Current expense (benefit) provision			
Ireland	\$ (5,368)	\$ 14,413	\$ (1,233)
U.S. – Federal and State	44,382	18,418	(4,663)
Other foreign	892	1,597	1,257
Total current expense (benefit) provision	39,906	34,428	(4,639)
Deferred benefit provision			
Ireland	\$ 22,801	\$ (15,844)	\$ (556,370)
U.S. – Federal and State	(120,532)	(824)	(7,581)
Other foreign	(13,839)	(5,911)	(24,654)
Total deferred benefit	(111,570)	(22,579)	(588,605)
Total (benefit) expense for income taxes	\$ (71,664)	\$ 11,849	\$ (593,244)

Total benefit for income taxes was \$71.7 million and \$593.2 million for the years ended December 31, 2021 and 2019, respectively, and total expense for income taxes was \$11.8 million for the year ended December 31, 2020. The current tax expense of \$39.9 million for the year ended December 31, 2021 was primarily attributable to the U.S. federal tax liability arising on U.S. taxable income generated from an intercompany transfer and license of intellectual property from a U.S. subsidiary to an Irish subsidiary. Due to the restrictions imposed by Section 7874 of the Code, the Company could not utilize its tax attributes such as net operating losses and tax credits to reduce its U.S. federal tax liability below the minimum tax required under Section 7874, therefore the Company recorded a U.S. federal tax provision of \$48.0 million in relation to the intercompany transfer and license of intellectual property. The deferred tax benefit of \$111.6 million for the year ended December 31, 2021, was primarily attributable to a tax benefit of \$49.2 million recognized due to a reduction in the state tax rate expected to apply to the reversal of temporary differences between the book values and tax bases of certain assets acquired through the Viela acquisition and tax benefit recognized on intercompany inventory transfers of \$13.9 million.

A reconciliation between the Irish statutory income tax rate to the Company's effective tax rate for 2021, 2020 and 2019 is as follows (in thousands):

	For the Years Ended December 31,		
	2021	2020	2019
Irish income tax at statutory rate (12.5%)	\$ 57,853	\$ 50,206	\$ (2,528)
Share-based compensation	(71,151)	(23,793)	(4,614)
Change in U.S. state effective tax rate	(49,388)	(1,737)	(1,551)
Foreign tax rate differential	(44,650)	(46,382)	14,111
Intercompany inventory transfers	(13,869)	(5,918)	(24,654)
U.S. federal and state tax credits	(11,551)	(13,809)	(16,752)
U.S. state income taxes	(6,798)	724	(135)
Uncertain tax positions	(5,150)	1,593	(382)
Notional interest deduction	—	—	(19,982)
Disallowed interest	—	236	1,749
Non-deductible in-process research and development costs	—	9,475	—
Write-off of United States deferred tax asset related to interest expense due to Anti-Hybrid Rules	—	15,250	—
Change in valuation allowances	1,667	4,183	4,069
Other non-deductible expenses	4,880	1,440	1,757
Intercompany transfer and license of IP assets	18,700	5,193	(553,334)
Disqualified compensation expense	47,050	14,601	7,219
Other, net	743	587	1,783
(Benefit) expense for income taxes	\$ (71,664)	\$ 11,849	\$ (593,244)
Effective income tax rate	(15.4)%	3.0%	(2933.5)%

The overall effective income tax rate for 2021 of (15.4)% was a lower rate than the Irish statutory rate of 12.5% primarily attributable to the excess tax benefits recognized on share-based compensation of \$71.2 million, a tax benefit of \$49.4 million recognized due to a reduction in the state tax rate expected to apply to the reversal of temporary differences between the book values and tax bases of certain assets acquired through the Viela acquisition, a tax benefit of \$44.7 million recognized on the pre-tax income and losses generated in jurisdictions with statutory tax rates different than the Irish statutory tax rate, a \$13.9 million tax benefit recognized on intercompany inventory transfers, and \$11.6 million of U.S. Federal and state tax credits generated during the year. These tax benefits are partially offset by an increase of \$47.1 million in non-deductible officers' compensation and a tax expense of \$18.7 million generated from an intercompany transfer and license of intellectual property from a U.S. subsidiary to an Irish subsidiary.

The overall effective income tax rate for 2020 of 3.0% was a lower rate than the Irish statutory rate of 12.5% primarily attributable to a tax benefit of \$46.4 million recognized on the pre-tax income and losses generated in jurisdictions with statutory tax rates different than the Irish statutory tax rate, the excess tax benefits recognized on share-based compensation of \$23.8 million and \$13.8 million of U.S. Federal and state tax credits generated during the year. These tax benefits are partially offset by tax expense of \$15.2 million recorded following the publication by the United States Department of Treasury and the Internal Revenue Service of the Final Regulations on the Anti-Hybrid Rules to write off a deferred tax asset related to certain interest expense accrued to a foreign related party, a tax expense of \$14.6 million on non-deductible officers' compensation and tax expense of \$9.5 million on non-deductible IPR&D expenses recorded in connection with the acquisition of Curzion.

The overall effective income tax rate for 2019 of 2,933.5% was a higher benefit rate than the Irish statutory rate of 12.5% primarily attributable to the recognition of a \$553.3 million deferred tax asset resulting from an intercompany transfer of intellectual property assets to an Irish subsidiary, a \$24.7 million tax benefit recognized on intercompany inventory transfers, a \$20.0 million tax benefit recognized on the Company's notional interest deduction, \$16.8 million of U.S. Federal and state tax credits generated during the year (inclusive of the deferred credit amortization) and the excess tax benefits recognized on share-based compensation of \$4.6 million. These tax benefits are partially offset by tax expense of \$14.1 million on the pre-tax income and losses generated in jurisdictions with statutory tax rates different than the Irish statutory tax rate, a tax expense of \$7.2 million on non-deductible officers' compensation and a tax expense of \$4.1 million on increases in net valuation allowances.

The change in the effective income tax rate in 2021 compared to that in 2020 was primarily due to an increase in excess tax benefits recognized on share-based compensation, a tax benefit of \$49.4 million recognized during the year ended December 31, 2021 due to a reduction in the state tax rate expected to apply to the reversal of temporary differences between the book values and tax bases of certain assets acquired through the Viela acquisition and an increase in tax benefit recognized on intercompany inventory transfers. These increases in benefit were partially offset by an increase in tax expense on non-deductible officers' compensation and a decrease in the tax benefit recognized on the pre-tax income and losses generated in jurisdictions with statutory tax rates different than the Irish statutory tax rate.

The change in the effective income tax rate in 2020 compared to that in 2019 was primarily due to the recognition of a deferred tax asset of \$553.3 million resulting from an intercompany transfer of intellectual property assets to an Irish subsidiary during the year ended December 31, 2019.

Significant components of the Company's net deferred tax assets and liabilities, are as follows (in thousands):

	As of December 31,	
	2021	2020
Deferred tax assets:		
Net operating loss carryforwards	\$ 75,431	\$ 34,258
Accrued compensation	60,827	54,770
U.S. federal and state credits	47,312	17,893
Accruals and reserves	37,175	18,267
Intercompany interest	34,777	42,239
Intangible assets	—	362,599
Other	6,790	1,035
Total deferred tax assets	262,312	531,061
Valuation allowance	(37,672)	(33,985)
Deferred tax assets, net of valuation allowance	\$ 224,640	\$ 497,076
Deferred tax liabilities:		
Intangible assets	\$ 67,321	\$ —
Property, plant and equipment	8,614	1,438
Debt discount	1,062	1,271
Total deferred tax liabilities	76,997	2,709
Net deferred income tax asset	\$ (147,643)	\$ (494,367)

No provision has been made for income taxes on undistributed earnings of subsidiaries because it is the Company's intention to indefinitely reinvest outside of Ireland undistributed earnings of its subsidiaries. In the event of the distribution of those earnings to Ireland in the form of dividends, a sale of the subsidiaries, or certain other transactions, the Company may be liable for income taxes in Ireland. The cumulative unremitted earnings of the Company as of December 31, 2021, were approximately \$4.6 billion, and the Company estimates that it would incur approximately \$179.4 million of additional income tax on unremitted earnings were they to be remitted to Ireland.

As of December 31, 2021, the Company had net operating loss carryforwards of approximately \$223.5 million for U.S. federal, \$32.6 million for various U.S. states and \$6.2 million for non-U.S. losses. Net operating loss carryforwards for U.S. federal income tax purposes that were generated prior to January 1, 2018, have a twenty-year carryforward life and the earliest layers will begin to expire in 2031. U.S. state net operating losses will start to expire in 2023 for the earliest net operating loss layers to the extent there is not sufficient state taxable income to utilize those net operating loss carryovers. Irish net operating losses may be carried forward indefinitely and therefore have no expiration. Utilization of the U.S. net operating loss carryforwards may be subject to annual limitations as prescribed by federal and state statutory provisions. The imposition of the annual limitations may result in a portion of the net operating loss carryforwards expiring unused.

Utilization of certain net operating loss and tax credit carryforwards in the United States is subject to an annual limitation due to ownership change limitations provided by Sections 382 and 383 of the Internal Revenue Code. Certain net operating losses generated before an August 2, 2012 ownership change and federal net operating losses and federal tax credits acquired through the Viela acquisition are subject to an annual limitation. The U.S. federal net operating loss carryforward and U.S. federal tax credit carryforward limitation is cumulative such that any use of the carryforwards below the limitation in a particular tax year will result in a corresponding increase in the limitation for the subsequent tax year.

At December 31, 2021, the Company had \$37.8 million and \$19.2 million of U.S. federal and state income tax credits, respectively, to reduce future tax liabilities. The federal income tax credits consisted primarily of R&D credits. The U.S. state income tax credits consisted primarily of California R&D credits and the Illinois Economic Development for a Growing Economy ("EDGE") tax credits. The U.S. federal R&D credits have a twenty-year carryforward life and will begin to expire in 2038. The California R&D credits have indefinite lives and therefore are not subject to expiration. The EDGE credits have a five-year carryforward life following the year of generation and will begin to expire in 2022.

A reconciliation of the beginning and ending amounts of valuation allowances for the years ended December 31, 2021, 2020 and 2019 is as follows (in thousands):

Valuation allowances at December 31, 2018	\$	(26,472)
Increase for 2019 activity		(5,693)
Release of valuation allowances		2,897
Valuation allowances at December 31, 2019	\$	(29,268)
Increase for 2020 activity		(8,841)
Release of valuation allowances		4,124
Valuation allowances at December 31, 2020	\$	(33,985)
Increase for 2021 activity		(5,181)
Release of valuation allowances		1,494
Valuation allowances at December 31, 2021	\$	(37,672)

Deferred tax valuation allowances increased by \$3.7 million, \$4.7 million and \$2.8 million during the years ended December 31, 2021, 2020 and 2019, respectively. For the year ended December 31, 2021, the net increase in valuation allowances resulted primarily from additional U.S. state tax credits, state net operating losses and a non-U.S. capital loss which are unlikely to be realized in the foreseeable future, partially offset by the release of a portion of the valuation allowance with respect to Illinois EDGE tax credits which expired unused. The Company continues to carry its deferred tax asset established in Ireland, which was recognized at the end of 2019, pursuant to an intercompany transfer of intellectual property assets. The Company has evaluated the need for a valuation allowance with respect to this deferred tax asset, and as part of that analysis, the Company reviewed its projected earnings in the foreseeable future. Based upon all available evidence, it is more likely than not that the Company would be able to fully realize the tax benefit on the deferred tax asset resulting from the intercompany transfer of intellectual property assets.

The changes in the Company's uncertain income tax positions for the years ended December 31, 2021, 2020 and 2019, excluding interest and penalties, consisted of the following (in thousands):

	For the Years Ended		
	December 31,		
	2021	2020	2019
Beginning balance – uncertain tax positions	\$ 29,431	\$ 27,428	\$ 26,306
Tax positions in the year:			
Additions	3,838	3,837	2,553
Acquired uncertain tax positions	4,220	—	—
Tax positions related to prior years:			
Additions	—	—	1,663
Settlements and lapses	(9,042)	(1,834)	(3,094)
Ending balance – uncertain tax positions	\$ 28,447	\$ 29,431	\$ 27,428

For the year ended December 31, 2021, the net decrease in uncertain tax positions was primarily attributable to lapses in statute for a portion of uncertain tax positions in jurisdictions outside of the United States, uncertain tax positions relating to U.S. federal R&D and orphan drug credits and uncertain tax positions in relation to U.S. state tax filings. These decreases were partially offset by uncertain tax positions related to U.S. federal R&D and orphan drug credits acquired as part of the Viela acquisition and additional uncertain tax positions recognized on U.S. federal R&D and orphan drug credits generated during the year. In the Company's consolidated balance sheet, uncertain tax positions (including interest and penalties) of \$21.0 million were included in other long-term liabilities, and an additional \$8.7 million was included in deferred tax assets.

At December 31, 2021, penalties of \$0.3 million and interest of \$1.4 million are included in the balance of the uncertain tax positions and penalties of \$0.3 million and interest of \$1.5 million were included in the balance of uncertain tax positions at December 31, 2020. The Company classifies interest and penalties with respect to income tax liabilities as a component of income tax expense. The Company assessed that its liability for uncertain tax positions will not significantly change within the next twelve months. If these uncertain tax positions are released, the impact on the Company's tax provision would be a benefit of \$29.7 million, including interest and penalties.

The Company files income tax returns in Ireland, in the United States for federal and various states, as well as in certain other jurisdictions. At December 31, 2021, open tax years in U.S. federal and certain state jurisdictions date back to 2007 due to the taxing authorities' ability to adjust operating loss carryforwards. In Ireland, the statute of limitations expires five years from the end of the tax year or four years from the time a tax return is filed, whichever is later. Therefore, the earliest year open to examination is 2017 with the lapse of statute occurring in 2022. No changes in settled tax years have occurred to date.

NOTE 20 – EMPLOYEE BENEFIT PLANS

U.S. Retiree Medical Plan

The Company implemented a new retiree medical plan effective October 1, 2021, which provides certain medical benefits to eligible retirees in the United States.

The following table summarizes the changes in benefit obligation as of December 31, 2021, for this plan (in thousands):

	2021
Benefit obligation at beginning of year	\$ —
Prior service cost at initiation of plan	15,625
Service cost	1,166
Interest cost	113
Actuarial loss	16
Benefits paid net of participant contributions	(14)
Benefit obligation at end of year	\$ 16,906

As of December 31, 2021, the unfunded status for the retiree medical plan was \$16.9 million.

The following table summarizes the amounts recognized in the consolidated balance sheet as of December 31, 2021, for this plan (in thousands):

	2021
Accrued expenses and other current liabilities	\$ (83)
Other long-term liabilities	(16,823)
Amounts recognized on the consolidated balance sheet	\$ (16,906)

The following table summarizes the amounts recognized in accumulated other comprehensive loss as of December 31, 2021, for this plan (in thousands):

	2021
Prior service cost	\$ 15,300
Actuarial loss	16
Accumulated other comprehensive loss before income taxes	\$ 15,316

Expected Benefit Payments

The following table summarizes total benefit payments, which reflect expected future service, expected to be paid to plan participants (in thousands):

2022	\$ 83
2023	215
2024	383
2025	627
2026	975
2027 to 2031	10,450

Components of Net Periodic Benefit Cost and Amounts Recognized in Other Comprehensive Loss

The following table summarizes net period benefit cost recognized and the amounts recognized in other comprehensive loss for the year ended December 31, 2021 (in thousands):

	<u>2021</u>
Service cost	\$ 1,166
Interest cost	113
Amortization of prior service cost	<u>325</u>
Net periodic benefit cost	1,604
Prior service cost	15,625
Amortization of prior service cost	(325)
Actuarial loss	<u>16</u>
Total recognized in other comprehensive loss	15,316
Total recognized in net periodic benefit cost and other comprehensive loss	\$ 16,920

The components of net periodic benefit cost other than service cost are included in other income (expense), net in the consolidated statement of comprehensive income.

Weighted-Average Actuarial Assumptions

The following table summarizes weighted-average assumptions used to determine net periodic benefit cost and the benefit obligation as of December 31, 2021:

	<u>2021</u>
Discount rate for net periodic benefit cost	2.89%
Discount rate for benefit obligation	2.89%

Health Care Cost Trend Rates

The following table summarizes assumed health care cost trend rates as of December 31, 2021:

Net periodic benefit cost	<u>2021</u>
Health care cost trend rate assumed for next year	6.29%
Rate to which the cost trend rate is assumed to decline (the ultimate trend rate)	4.44%
Year that the rate reaches the ultimate trend rate	2030

Other Employee Benefit Plans

The Company sponsors a defined contribution 401(k) retirement savings plan covering all of its U.S. employees, whereby an eligible employee may elect to contribute a portion of his or her salary on a pre-tax basis, subject to applicable federal limitations. The Company is not required to make any discretionary matching of employee contributions. The Company makes a matching contribution equal to 100% of each employee's elective contribution to the plan of up to 3% of the employee's eligible pay, and 50% for the next 2% of the employee's eligible pay. The full amount of this employer contribution is immediately vested in the plan. For the years ended December 31, 2021, 2020 and 2019, the Company recorded defined contribution expense of \$16.8 million, \$12.0 million and \$6.2 million, respectively.

The Company's wholly owned Irish subsidiary sponsors a defined contribution plan covering all of its employees in Ireland. For the years ended December 31, 2021, 2020 and 2019, the Company recognized expenses of \$1.1 million, \$0.8 million and \$0.6 million, respectively, under this plan.

The Company has a non-qualified deferred compensation plan for executives. The deferred compensation plan obligations are payable in cash upon retirement, termination of employment and/or certain other times in a lump-sum distribution or in installments, as elected by the participant in accordance with the plan. As of December 31, 2021 and 2020, the deferred compensation plan liabilities totaled \$26.5 million and \$18.4 million, respectively, and are included in "other long-term liabilities" in the consolidated balance sheet. The Company held funds of approximately \$26.5 million and \$18.4 million in an irrevocable grantor's rabbi trust as of December 31, 2021 and 2020, respectively, related to this plan. Rabbi trust assets are classified as trading marketable securities and are included in "other current assets" in the consolidated balance sheets. Unrealized gains and losses on these marketable securities are included in "other income (expense)" in the consolidated statements of comprehensive income. For the years ended December 31, 2021, 2020 and 2019, the Company recognized expenses of \$2.3 million, \$1.1 million and \$1.1 million, respectively, under this plan.

SCHEDULE II – VALUATION AND QUALIFYING ACCOUNTS

For Each of the Three Fiscal Years Ended December 31, 2021, 2020 and 2019:

Valuation and Qualifying Accounts (in thousands)	Balance at beginning of period	Acquisitions	Additions charged to costs and expenses	Deductions from reserves	Balance at end of period
Year ended December 31, 2021:					
Allowance for returns	40,918	—	17,573	(24,609)	33,882
Allowance for prompt pay discounts	5,180	162	41,426	(42,980)	3,788
Year ended December 31, 2020:					
Allowance for returns	45,082	—	16,446	(20,610)	40,918
Allowance for prompt pay discounts	7,189	—	45,886	(47,895)	5,180
Year ended December 31, 2019:					
Allowance for returns	39,041	—	25,813	(19,772)	45,082
Allowance for prompt pay discounts	9,113	—	64,968	(66,892)	7,189

SIGNATURES

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

HORIZON THERAPEUTICS PLC

Dated: March 1, 2022

By: /s/ TIMOTHY P. WALBERT
Timothy P. Walbert

President, Chief Executive Officer and
Chairman of the Board

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Timothy P. Walbert and Paul W. Hoelscher, and each of them, his or her true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution, for him or her and in his or her name, place and stead, in any and all capacities, to sign any and all amendments (including post-effective amendments) to this report, and to file the same, with all 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 in connection 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, or either of them, or their or his or her substitutes or substitute, may lawfully do or cause to be done by virtue hereof.

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

<u>SIGNATURE</u>	<u>TITLE</u>	<u>DATE</u>
<u>/s/ TIMOTHY P. WALBERT</u> Timothy P. Walbert	President, Chief Executive Officer and Chairman of the Board (<i>Principal Executive Officer</i>)	March 1, 2022
<u>/s/ PAUL W. HOELSCHER</u> Paul W. Hoelscher	Executive Vice President and Chief Financial Officer (<i>Principal Financial Officer</i>)	March 1, 2022
<u>/s/ MILES W. MCHUGH</u> Miles W. McHugh	Senior Vice President and Chief Accounting Officer (<i>Principal Accounting Officer</i>)	March 1, 2022
<u>/s/ MICHAEL GREY</u> Michael Grey	Director	March 1, 2022
<u>/s/ WILLIAM F. DANIEL</u> William F. Daniel	Director	March 1, 2022
<u>/s/ JEFF HIMAWAN</u> Jeff Himawan, Ph.D.	Director	March 1, 2022
<u>/s/ SUSAN MAHONY</u> Susan Mahony, Ph.D.	Director	March 1, 2022
<u>/s/ GINO SANTINI</u> Gino Santini	Director	March 1, 2022
<u>/s/ JAMES SHANNON</u> James Shannon, M.D.	Director	March 1, 2022
<u>/s/ H. THOMAS WATKINS</u> H. Thomas Watkins	Director	March 1, 2022
<u>/s/ PASCALE WITZ</u> Pascale Witz	Director	March 1, 2022

Board of Directors

Timothy P. Walbert

Chairman, President and Chief Executive Officer
Horizon Therapeutics plc

Michael Grey

Lead Independent Director,
Horizon Therapeutics plc
Chairman, Mirum Pharmaceuticals, Inc.

William F. Daniel

Chairman, Malin Corporation plc

Jeff Himawan, Ph.D.

Managing Director, Essex Woodlands Health Ventures, L.P.

Susan Mahony, Ph.D.

Director, Zymeworks Inc.

Gino Santini

Director, Intercept Pharmaceuticals, Inc.

James Shannon, M.D.

Chairman, MannKind Corporation

H. Thomas Watkins

Lead Independent Director, Vanda Pharmaceuticals Inc.

Pascale Witz

Director, PerkinElmer Inc.

Company Information

Corporate Headquarters

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Horizontherapeutics.com

Ordinary Shares

Horizon Therapeutics plc ordinary shares are traded on the Nasdaq Global Market under the symbol "HZNP."

Annual General Meeting

The annual general meeting of shareholders will be held at 3 p.m. local time on April 28, 2022, at: Horizon Therapeutics plc Corporate Headquarters, 70 St. Stephen's Green, Dublin 2, D02 E2X4, Ireland

Independent Registered Public Accounting Firm

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Investor Relations

investor-relations@horizontherapeutics.com

SEC Form 10-K

A copy of our annual report on Form 10-K filed with the Securities and Exchange Commission is available without charge by calling or writing to our corporate headquarters address provided above.

