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

FORM 10-K

☒ **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 000-19319

Vertex Pharmaceuticals Incorporated

(Exact name of registrant as specified in its charter)

Massachusetts	**04-3039129**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
50 Northern Avenue, Boston, Massachusetts	**02210**
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code **(617) 341-6100**

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

Title of Each Class	**Trading Symbol**	**Name of Each Exchange on Which Registered**
Common Stock, $0.01 Par Value Per Share	VRTX	The Nasdaq Global Select Market

Securities registered pursuant to Section 12(g) of the Exchange 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 Exchange Act. Yes ☐ No ☒

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

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

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

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

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

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

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

The aggregate market value of the registrant's common stock held by non-affiliates of the registrant based on the closing price on June 30, 2021 (the last business day of the registrant's most recently completed second fiscal quarter of 2021) was $51.6 billion.

As of January 31, 2022, the registrant had 254,576,691 shares of common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the definitive proxy statement for the 2022 Annual Meeting of Shareholders, which we expect to hold on May 18, 2022, are incorporated by reference into Part III of this Annual Report on Form 10-K.

VERTEX PHARMACEUTICALS INCORPORATED

ANNUAL REPORT ON FORM 10-K

TABLE OF CONTENTS

"Vertex," "we," "us" and "our" as used in this Annual Report on Form 10-K refer to Vertex Pharmaceuticals Incorporated, a Massachusetts corporation, and its subsidiaries.

"VERTEX®," "KALYDECO®," "ORKAMBI®," "SYMDEKO®," "SYMKEVI®" and "TRIKAFTA®" are registered trademarks of Vertex. The trademark for "KAFTRIO" is pending in the United States and registered in the European Union. Other brands, names and trademarks contained in this Annual Report on Form 10-K are the property of their respective owners.

We use the brand name for our products when we refer to the product that has been approved and with respect to the indications on the approved label. Otherwise, including in discussions of our cystic fibrosis development programs, we refer to our compounds by their scientific (or generic) name or VX developmental designation.

This Annual Report on Form 10-K contains forward-looking statements. Words such as "anticipates," "may," "forecasts," "expects," "intends," "plans," "potentially," "believes," "seeks," "estimates," variations of such words and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. Please refer to "Special Note Regarding Forward-Looking Statements" set forth in Part I, Item 1A, for a discussion of our forward-looking statements and the related risks and uncertainties of such statements.

PART I

ITEM 1. BUSINESS

OVERVIEW

We are a global biotechnology company that invests in scientific innovation to create transformative medicines for people with serious diseases with a focus on specialty markets. We have multiple approved medicines that treat the underlying cause of cystic fibrosis, or CF, a life-threatening genetic disease, and we have several ongoing clinical and research programs to advance and extend treatment of CF. Beyond CF, we have a pipeline of investigational therapies in other serious diseases where we are leveraging insight into causal human biology, including sickle cell disease, beta thalassemia, APOL1-mediated kidney disease, type 1 diabetes, pain, alpha-1 antitrypsin deficiency, and muscular dystrophies.

Marketed Products

Our goal in CF is to develop treatment regimens that will provide benefits to all people with CF and will enhance the benefits currently provided to people taking our medicines. Our marketed medicines are TRIKAFTA/KAFTRIO (elexacaftor/tezacaftor/ivacaftor and ivacaftor), SYMDEKO/SYMKEVI (tezacaftor/ivacaftor and ivacaftor), ORKAMBI (lumacaftor/ivacaftor) and KALYDECO (ivacaftor). Collectively, our four medicines are being used to treat the majority of the approximately 83,000 people with CF in North America, Europe and Australia.

We are focused on increasing the number of people with CF eligible and able to receive our medicines through label expansions, approval of new medicines, and expanded reimbursement. We are evaluating our current medicines in additional patient populations, including younger children, with the goal of having small molecule treatments for approximately 90% of people with CF.

Research and Development

Our strategy is to discover and develop innovative medicines by combining transformative advances in the understanding of human disease biology and in the science of therapeutics. This research and early development strategy includes advancing multiple compounds from each program into early clinical trials and evaluating the resulting patient data to inform the discovery and development of additional compounds, with the goal of bringing first-in-class and best-in-class therapies to patients. Our strategy and approach are intended to increase the likelihood of successfully bringing transformative medicines to patients, and to provide durable clinical and commercial success. We are advancing programs across multiple disease areas and modalities, including:

- *Cystic Fibrosis.* We are evaluating in Phase 3 clinical trials a new, once-daily investigational triple combination of VX-121/tezacaftor/VX-561 (deutivacaftor). We also are researching genetic therapies and gene-editing approaches to treat the remaining approximately 10% of people with CF who are not expected to benefit from our small molecule medicines.
- *Sickle Cell Disease and Beta Thalassemia.* We are evaluating in Phase 3 clinical trials CTX001, an investigational CRISPR/Cas9-based gene-editing therapy for severe sickle cell disease, or SCD, and transfusion-dependent beta thalassemia, or TDT, with CRISPR Therapeutics AG, or CRISPR. Enrollment is complete, and we anticipate regulatory submissions for CTX001 in late 2022.
- *APOL1-Mediated Kidney Disease.* Based on positive Phase 2 data for VX-147, our small molecule for the treatment of APOL1-mediated focal segmental glomerulosclerosis, or FSGS, we expect to advance VX-147 into pivotal development in a broader population of people with APOL1-mediated kidney disease, or AMKD, in the first quarter of 2022.
- *Type 1 Diabetes.* We are evaluating VX-880, a stem-cell derived islet cell therapy involving the transplantation of islet cells, for the potential treatment of type 1 diabetes, or T1D, in a Phase 1/2 clinical trial, and recently announced positive Day 150 data for the first T1D patient in this clinical trial. We will continue to dose patients in 2022. We also are pursuing additional programs in T1D, in which the implanted islet cells are encapsulated in an immunoprotective device or modified to produce hypoimmune cells.

- *Pain*. We are evaluating VX-548, a NaV 1.8 inhibitor, for the non-opioid treatment of acute pain in two Phase 2 clinical trials. We expect to have data from these clinical trials in the first quarter of 2022.
- *Alpha-1 Antitrypsin, or AAT, Deficiency.* We obtained proof-of-mechanism for VX-864 in a Phase 2 study of protein folding correction of the Z-AAT protein. We plan to advance into the clinic one or more novel small molecule correctors intended to address the lung and liver manifestations of AAT deficiency, or AATD, in 2022.
- *Duchenne muscular dystrophy, or DMD, and myotonic dystrophy type 1, or DM1*. We are focused on advancing gene-editing therapies aimed at treating the underlying cause of DMD and DM1. We are also exploring potential small molecule approaches to address the underlying causal biology for both DMD and DM1.
- In addition to the clinical stage programs listed above, we have a number of early-stage research programs aimed at other targets that represent the causal human biology of serious diseases.

We plan to continue investing in our research and development programs and fostering scientific innovation by identifying additional product candidates through our internal research efforts and investing in business development transactions to access emerging technologies, products and product candidates.

CYSTIC FIBROSIS

Background

CF is a life-shortening genetic disease caused by a defective or missing cystic fibrosis transmembrane conductance regulator, or CFTR, protein resulting from mutations in the CFTR gene. To develop CF, children must inherit two defective CFTR genes, which are referred to as alleles; one allele is inherited from each parent. The vast majority of patients with CF carry at least one F508del mutation. The F508del mutation results in a defect in the CFTR protein in which the CFTR protein does not reach the surface of the cells in sufficient quantities and does not adequately transport chloride ions.

The absence of working CFTR proteins results in poor flow of salt and water into and out of cells in a number of organs, including the lungs. As a result, thick, sticky mucus builds up and blocks the passages in many organs, leading to a variety of symptoms. In particular, mucus builds up and clogs the airways in the lungs, causing chronic lung infections and progressive lung damage. CFTR potentiators such as ivacaftor and VX-561 increase the probability that the CFTR protein channels open on the cell surface, increasing the flow of salt and water into and out of the cell. CFTR correctors, such as lumacaftor, tezacaftor, and elexacaftor, help CFTR proteins reach the cell surface.

Our Medicines

Our medicines are collectively being used by the majority of people with CF in North America, Europe and Australia. Our approved medicines, including information regarding the indication and age groups for which the medicine is approved, are set forth in the table below.

Product	Scientific Name	Region/Initial Approval [(1)]	Indication	Eligible Age Group
trikafta®	elexacaftor/tezacaftor/ivacaftor and ivacaftor	U.S. (2019)	People with CF with (i) at least one F508del mutation, or (ii) another mutation that is responsive to elexacaftor/tezacaftor/ivacaftor and ivacaftor	6 years of age and older
kaftrio®	elexacaftor/tezacaftor/ivacaftor and ivacaftor	E.U. (2020)	People with CF with at least one F508del mutation	6 years of age and older
symdeko®	tezacaftor/ivacaftor and ivacaftor	U.S. (2018)	People with CF (i) homozygous for the F508del mutation or (ii) with at least one mutation that is responsive to tezacaftor/ivacaftor	6 years of age and older
symkevi®	tezacaftor/ivacaftor	E.U. (2018)	People with CF (i) homozygous for the F508del mutation or (ii) with one copy of the F508del mutation and one copy of certain mutations that result in residual CFTR activity	6 years of age and older
ORKAMBI®	lumacaftor/ivacaftor	U.S. (2015)	People with CF homozygous for the F508del mutation	2 years of age and older
	lumacaftor/ivacaftor	E.U. (2015)	People with CF homozygous for the F508del mutation	2 years of age and older
kalydeco®	ivacaftor	U.S. (2012)	People with CF with a mutation that is responsive to ivacaftor	4 months of age and older
	ivacaftor	E.U. (2012)	People with CF with R117H mutation or one of certain gating mutations	4 months of age and older

(1) At the end of the Brexit transition period on January 1, 2021, the Medicines and Healthcare products Regulatory Agency, or MHRA, in Great Britain approved licenses for supply of each product in England, Scotland and Wales. The existing European Medicines Agency, or EMA, licenses continue to authorize supply in Northern Ireland.

In addition to the European Union, or the E.U. and the United States, or the U.S., we market our products in additional countries, including the United Kingdom, or the U.K., Australia, Switzerland, Israel, and Canada. We continuously seek to increase the number of patients eligible and able to receive our current medicines through label expansions, approval of new medicines and expanded reimbursement. Since the beginning of 2021, events that have resulted from our efforts include:

- The U.S. Food and Drug Administration, or the FDA, approved the use of TRIKAFTA for children with CF 6 through 11 years of age who have at least one F508del mutation or at least one other mutation that is responsive to TRIKAFTA.
- Health Canada granted marketing authorization for TRIKAFTA for people with CF 12 years of age and older who have at least one F508del mutation. Our application for approval of TRIKAFTA for children 6 through 11 years of age has been accepted for priority review by Health Canada.

- In January 2022, the European Commission and the MHRA granted marketing authorization for KAFTRIO for the treatment of children with CF 6 through 11 years of age who have at least one F508del mutation in the CFTR gene.
- TRIKAFTA/KAFTRIO is now approved and reimbursed or accessible in more than 20 countries outside the U.S.

RESEARCH AND DEVELOPMENT PROGRAMS

We invest in research and development to discover and develop transformative medicines for people with serious diseases, with a focus on specialty markets. Our research strategy is to combine transformative advances in the understanding of human disease biology and the science of therapeutics to discover and develop new medicines. Our approach to drug discovery has been validated through our success in moving novel small molecule product candidates into clinical trials and obtaining marketing approvals for TRIKAFTA/KAFTRIO, KALYDECO, ORKAMBI, and SYMDEKO/SYMKEVI for the treatment of CF and INCIVEK (telaprevir) for the treatment of hepatitis C infection. In addition, we have achieved clinical proof-of-concept for gene-editing of BCL11A for the treatment of beta thalassemia and SCD, for APOL1 inhibition to decrease proteinuria in patients with APOL1-mediated kidney disease, and for NaV1.8 inhibition in the treatment of three different pain models.

We continue to research and develop small molecule product candidates for the treatment of serious diseases, including CF, APOL1-mediated kidney disease, pain, AATD, DMD and DM1. Our research and development approach includes advancing multiple candidates into clinical trials, pursuing multiple modalities and evaluating clinical and non-clinical data to inform drug discovery and development, with the goal of bringing best-in-class therapies to patients.

Over the last several years, we have expanded our capabilities to include additional innovative therapeutic modalities with a focus on cell and genetic therapies, which have the potential to treat, and in some cases, cure diseases by addressing the underlying cause of the disease. We have increased our internal investment in cell and genetic therapies, including establishment of a new research and development site in Boston, Massachusetts focused primarily on cell and genetic therapies. In addition, we have made several significant investments in external innovation, including:

- our collaborations with CRISPR to access and develop therapeutics based on the CRISPR gene-editing technology, including an agreement under which we now lead the worldwide development, manufacturing and commercialization of CTX001;
- our establishment of cell therapy programs for T1D through our acquisition of Semma;
- our establishment of genetic therapy programs for DMD and DM1, through our acquisition of Exonics; and
- our collaboration with Moderna, Inc., or Moderna, for the discovery and development of lipid nanoparticles and mRNAs that can deliver gene-editing therapies.

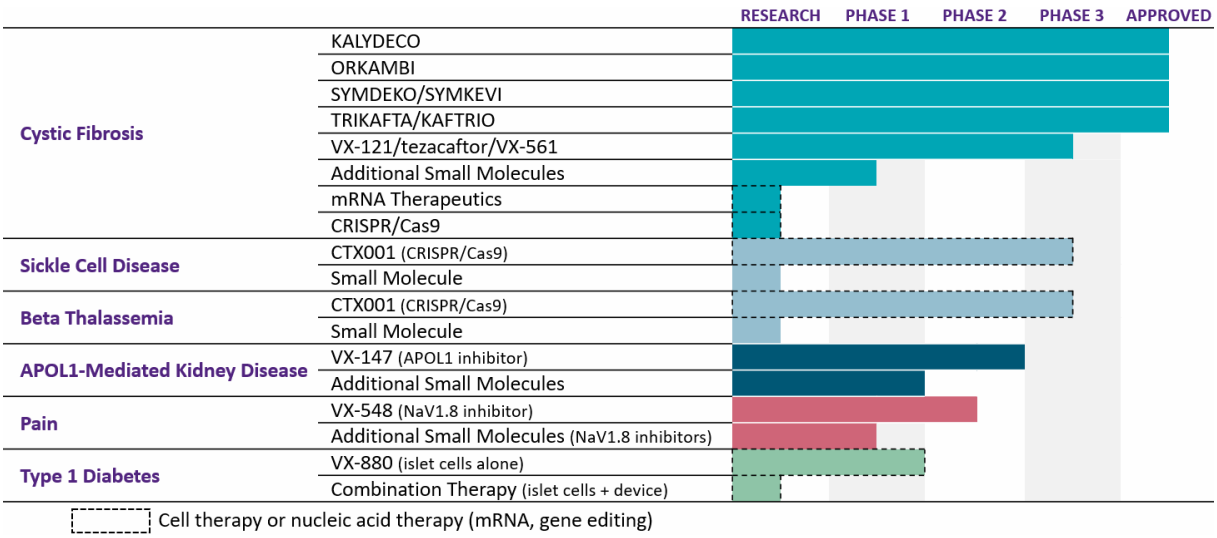
The experience we gained developing medicines for CF and our analysis of research and development programs conducted by other companies in our industry have shaped a disciplined strategy that guides our investments in research and development and external innovation that focuses on:

- transformative treatments for life-threatening diseases with a high unmet medical need;
- targets validated as playing a causal role in the human biology of a disease;
- innovative therapeutic approaches to addressing those targets;
- biological assays and clinical biomarkers designed to predict clinical responses; and
- efficient clinical and regulatory paths to bring new medicines to patients.

To augment our internal programs, we plan to continue acquiring businesses and technologies and collaborating with biopharmaceutical and technology companies, leading academic research institutions, government laboratories, foundations and other organizations to advance research in our areas of therapeutic interest, as well as to access technologies needed to execute on our strategy. We have established such relationships with organizations around the world and intend to extend and leverage that experience to further our research efforts to discover transformational medicines for serious diseases. We will

continue to identify and evaluate potential acquisitions and collaborations that may be similar to or different from the transactions that we have engaged in previously.

The following chart represents our pipeline programs by disease area, stage of development, and modality, for programs that have lead assets in the clinic.



CF Pipeline

We have initiated Phase 3 clinical trials evaluating a once-daily investigational triple combination of VX-121/tezacaftor/VX-561 (deutivacaftor). Clinical and preclinical data indicate that this triple combination has the potential to provide enhanced benefit beyond TRIKAFTA/KAFTRIO for people with CF who have the F508del mutation on at least one allele. Our Phase 3 program consists of two 52-week clinical trials, which will evaluate the safety and efficacy of the new combination relative to TRIKAFTA in a total of 950 people with CF. Both clinical trials will measure the regulatory-enabling endpoint of absolute change in ppFEV1, a measure of lung function, that will be analyzed for non-inferiority to TRIKAFTA. The clinical trials also are designed to assess the absolute change from baseline in ppFEV1 and sweat chloride for superiority to TRIKAFTA. We continue to identify and develop additional CFTR modulators with the goal of achieving carrier levels of CFTR activity for approximately 90% of people with CF who respond to CFTR modulators.

We continue to research genetic therapies, such as messenger ribonucleic acid, or mRNA, and gene-editing approaches, to treat the remaining approximately 10% of people with CF who do not make CFTR protein and, as a result, are not expected to benefit from our small molecule medicines. In collaboration with Moderna, we are developing CF mRNA therapeutics designed to treat the underlying cause of CF for these people by enabling cells in the lungs to produce functional CFTR protein. We are conducting enabling studies and expect to submit an Investigational New Drug Application, or IND, for this program in 2022.

Sickle Cell Disease and Beta Thalassemia

SCD and beta thalassemia are hemoglobinopathies, a group of inherited blood disorders that result from gene mutations that alter hemoglobin, a protein in red blood cells that delivers oxygen throughout the body.

SCD is caused by the change of a single amino acid in the hemoglobin gene that causes red cells to change shape in settings of low oxygen. These sickled cells block blood flow and can lead to severe pain, organ damage, and shortened life span. Treatment is typically focused on relieving pain and minimizing organ damage, requiring medication and, for some patients, monthly blood transfusions and frequent hospital visits. We believe there are approximately 25,000 patients with severe SCD in the U.S. and Europe.

Beta thalassemia is caused by loss-of-function mutations in hemoglobin that lead to severe anemia in patients, which causes fatigue and shortness of breath. In infants, beta thalassemia causes failure to thrive, jaundice, and feeding problems. Complications of beta thalassemia can lead to an enlarged spleen, liver and/or heart, misshapen bones and delayed puberty. Treatment for beta thalassemia varies depending on the disease severity for each patient. Patients with TDT, the most severe form of the disease, require regular blood transfusions, as frequently as every two to four weeks. Repeated blood transfusions eventually cause an unhealthy buildup of iron in the patient, leading to organ damage. We believe that there are approximately 7,000 patients with TDT in the U.S. and Europe.

We are developing CTX001, an investigational CRISPR/Cas9-based gene-editing therapy, for the treatment severe SCD and TDT, with our collaborator, CRISPR. Our therapeutic approach involves isolating hematopoietic stem and progenitor cells, or HSPCs, which give rise to red blood cells, from a patient, treating those cells ex vivo with CRISPR/Cas9 in order to modify the erythroid-specific enhancer in the BCL11A gene, and reintroducing the edited cells back into the patient. This approach has the potential to increase levels of fetal hemoglobin in erythrocytes and reduce or eliminate symptoms associated with disease.

We are investigating CTX001 in two Phase 3 open-label clinical trials designed to assess the safety and efficacy of a single dose of CTX001 in patients ages 12 to 35 with severe SCD (the CLIMB SCD-121 clinical trial) and TDT (the CLIMB THAL-111 clinical trial), respectively. Patients enrolled in the clinical trials first undergo a treatment that mobilizes a population of HSPCs from the bone marrow into the bloodstream. Blood cells are collected from the patient's bloodstream and transferred to a manufacturing facility where the HSPCs are purified and CRISPR/Cas9 gene-editing is performed. Following manufacturing, the edited cells, now called CTX001, are transferred back to the clinical site. Patients are preconditioned with a treatment that ablates their bone marrow prior to infusion of CTX001.

Data presented to date support the profile of CTX001 as a potential one-time functional cure for people with severe SCD and TDT. CTX001 safety data to date is generally consistent with an autologous stem cell transplant and myeloablative conditioning. Enrollment is complete in the ongoing clinical trials evaluating CTX001 in severe SCD and TDT. We anticipate regulatory submissions of CTX001 in late 2022.

APOL1-Mediated Kidney Disease

Inherited mutations in the APOL1 gene play a causal role in the biology of severe proteinuric kidney diseases referred to as AMKD. Patients with AMKD inherit two mutations in the APOL1 gene resulting in significant proteinuria, and are characterized by a high risk of progression to end stage renal disease. Among patients with AMKD are those with the histological finding of FSGS and co-morbidities such as hypertension. In AMKD, the kidney's filtering units known as the glomerulus, and specifically the cells known as podocytes, are damaged, leading to leakage of protein into the urine, deterioration in kidney function, scarring, and, ultimately, permanent kidney damage. We are evaluating multiple novel small molecules that inhibit the function of APOL1 protein with the potential to treat APOL1-mediated kidney disease, including APOL1-mediated FSGS.

In December 2021, we announced that patients with APOL1-mediated FSGS treated with VX-147 on top of standard of care achieved a statistically significant, substantial, and clinically meaningful reduction of proteinuria in a Phase 2 proof-of-concept clinical trial. VX-147 was well tolerated by patients. We anticipate completing our end of Phase 2 meetings with regulators and advancing VX-147 into pivotal development in people with APOL1-mediated kidney disease, including APOL1-mediated FSGS, in the first quarter of 2022.

Type 1 Diabetes

T1D is a chronic, metabolic disorder caused by an absence of insulin secretion by the beta cells in the pancreas. In patients with T1D, the insulin-producing islet cells of the pancreas are destroyed by the person's own immune system, resulting in a complete lack of insulin. While insulin therapy allows patients to live for decades with the disease, challenges of insulin therapy include inadequate control of blood sugar (both hyper- and hypo-glycemia), a substantial burden of care on patients and families, and long-term vascular complications.

We are developing autologous, fully differentiated stem-cell derived islet cell therapies designed to replace insulin-producing islet cells that are destroyed in people with T1D, with the goal of delivering a functional cure. We are pursuing three programs for the transplant of functional islets into patients: transplantation of islet cells alone, using immunosuppression to protect the implanted cells, implantation of the islet cells inside a novel immunoprotective device, and

development of hypoimmune cells to optimize how we protect the implanted islet cells from the immune system.

VX-880, our first program, is a stem cell-derived, allogeneic, fully differentiated, insulin-secreting islet cell replacement therapy, using standard immunosuppression to protect the implanted cells. Our Phase 1/2 clinical trial evaluating VX-880 as a potential treatment for T1D is ongoing at multiple clinical sites in the U.S. and a Clinical Trial Application has been approved in Canada. In January 2022, we announced positive Day 150 data for the first T1D patient in the Phase 1/2 clinical trial of VX-880, including restoration of islet cell function and rapid improvements in multiple measures. In this first patient, the safety of VX-880 was generally consistent with the immunosuppressive regimen used in this study. We will continue to dose patients in 2022.

In our second program, the stem cell-derived, fully differentiated, insulin-secreting islet cells are encapsulated and implanted in an immunoprotective device. In our third program, research in earlier stages is directed toward developing hypoimmune cells to further optimize how we protect the implanted islet cells from the immune system. We are conducting IND-enabling studies for the cells and device program, and we expect to submit an IND for this program in 2022.

Pain

Pain can be debilitating and develop from a variety of pathophysiological and psychological conditions. Patients with pain can suffer from acute pain (for example, following surgery or an injury), neuropathic pain (when there is damage to a nerve), and musculoskeletal pain. Current treatments may not work well and can cause significant side effects and the risk of addiction. In addition, there is the practice of over- and mis-utilization, as well as underutilization of current pain medicines.

The selective sodium channels NaV1.8 and NaV1.7 play unique roles in the pathophysiology of pain. We have discovered multiple inhibitors of NaV1.8 as potential treatments for pain and have obtained pharmacological validation of the potential of NaV1.8 inhibition with one of our first generation NaV1.8 inhibitors in three clinical pain models: acute pain, neuropathic pain, and musculoskeletal pain. VX-548 is a next generation NaV1.8 inhibitor. We are conducting two Phase 2 dose ranging acute pain clinical trials; one following bunionectomy surgery and the other following abdominoplasty surgery. We expect to have data from both clinical trials in the first quarter of 2022.

Alpha-1 Antitrypsin Deficiency

AATD is a severe disease of the liver and lung, caused by inherited mutations in the SERPINA1 gene that encodes the AAT protein. People who inherit two mutant SERPINA1 alleles (one from each parent) develop AATD. Most people who develop AATD have two copies of a single mutation known as the Z allele. The Z-AAT mutation results in a protein folding defect in the AAT protein leading the misfolded AAT protein to accumulate in the liver (where it is produced at high levels), which can cause liver damage. As a result, the protein fails to reach other organs in adequate quantity and function, particularly the lungs, where the AAT protein's normal role is to protect the lungs from the digestive effects of certain proteases. The unchecked activity of these proteases can cause auto-digestion of lung tissue and may lead to emphysema or chronic pulmonary obstructive disease, and lung infections over time. Currently, there is no cure or treatment that targets the underlying cause of the disease in both the liver and the lung. Available treatments are aimed at transiently increasing levels of AAT in the blood but have no effect in the liver. Patients living with AATD typically experience recurring hospital visits and a shortened life expectancy.

We seek to develop medicines that treat the underlying cause of AATD throughout the body. We have discovered multiple small molecule correctors that restore folding of the mutant AAT protein, leading to increased production of functional AAT protein. The restoration of AAT protein folding in the liver and of systemic AAT function has the potential to benefit both the liver and lung diseases caused by AATD. In June 2021, we announced that we had achieved our primary endpoint and established proof of mechanism in a Phase 2 clinical trial evaluating our Z-AAT corrector, VX-864, for the treatment of people with AATD who have two copies of the Z mutation. However, because the magnitude of treatment effect was unlikely to translate into substantial clinical benefit, we decided not to advance VX-864 into late-stage development. We continue to discover and develop additional molecules with increased potential to correct AATD, and we plan to advance one or more novel small molecule Z-AAT correctors into the clinic in 2022.

Duchenne Muscular Dystrophy and Myotonic Dystrophy Type 1

DMD and DM1 are inherited diseases that result in the weakening and breakdown of skeletal muscles over time. In 2019, we acquired Exonics and expanded our collaboration with CRISPR establishing preclinical programs to develop gene-editing therapies for DMD and DM1. We are focused on advancing gene-editing therapies aimed at treating the underlying cause of

DMD by restoring expression of near-full length dystrophin protein, and in DM1, by addressing the repeat expansion that causes the disease. Our collaboration with Affinia Therapeutics, Inc., or Affinia, enables access to a novel library of AAV capsids to support our ongoing research and development efforts in genetic therapies, including DMD and DM1. We also are exploring potential small molecule approaches for DMD and DM1.

COMMERCIALIZATION OF OUR MEDICINES

Commercial Organization

Our commercial organization focuses on supporting the appropriate use of TRIKAFTA/KAFTRIO, SYMDEKO/SYMKEVI, ORKAMBI and KALYDECO in the markets where these products have been approved. Our sales and marketing organizations are responsible for promoting products to health care providers, ensuring our products are distributed effectively, and obtaining reimbursement for our products from third-party payors, including governmental organizations in the U.S. and ex-U.S. markets. In the U.S., we sell our products primarily to a limited number of specialty pharmacy and specialty distributors. In international markets, we sell our products primarily to specialty distributors and retail chains, as well as hospitals and clinics, many of which are government-owned or supported.

Our U.S. field-based CF commercial team is comprised of a small number of individuals to support commercialization of our medicines for CF. We focus our CF marketing efforts in the U.S. on a relatively small number of physicians and health care professionals who write most of the prescriptions for CF medicines. Many of these physicians and health care professionals are located at a limited number of accredited centers in the U.S. focused on the treatment of CF. In international markets, we have small sales forces that support KALYDECO, ORKAMBI, SYMDEKO/SYMKEVI and TRIKAFTA/KAFTRIO in jurisdictions where these products are approved.

We market our products through personal interactions with physicians and allied health care professionals. In parallel, our government affairs and public policy group advocates for policies that promote life sciences innovation and increase awareness of the diseases on which we are focusing with state and federal legislatures, government agencies, public health officials and other policymakers. We also have established programs in the U.S. that provide our products to qualified uninsured or underinsured patients at no charge or at a reduced charge, based on specific eligibility criteria.

We continue to expand our commercial organization to prepare for launch readiness for future products from our pipeline programs and are focused on launch preparation activities for our CTX001 program, including building our teams focused on patient support, market access, and healthcare provider education, as well as those engaged in the coordination of treatment centers involved in the administration of CTX001.

Reimbursement

Sales of our products depend, to a large degree, on the extent to which our products will be reimbursed by third-party payors, such as government health programs, commercial insurance, and managed health care organizations. Increasingly, these third-party payors are becoming stricter in the ways they evaluate and reimburse medical products and services. Additionally, the containment of health care costs has become a priority of federal and state governments, and the prices of drugs have been a focus in this effort. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could limit our revenues. Decisions by third-party payors to not cover a product could reduce physician usage of the product.

Our CF medicines are broadly reimbursed by third-party payors in the U.S., including the federal government. We participate in the Medicaid Drug Rebate program, Medicare, and other governmental pricing programs. Medicaid is a joint federal and state program that is administered by the states for low-income and disabled beneficiaries. Under the Medicaid Drug Rebate program, we are required to pay a rebate to each state Medicaid program for our covered outpatient drugs that are dispensed to Medicaid beneficiaries as a condition of having federal funds being made available to the states for our drugs. Medicaid rebates are based on pricing data reported by us on a monthly and quarterly basis to the Centers for Medicare & Medicaid Services, or CMS, the federal agency that administers the Medicaid and Medicare programs.

Any company that participates in the Medicaid Drug Rebate program also must participate in the 340B drug pricing program, or the 340B program, and the Federal Supply Schedule, or FSS, pricing program. The 340B program, which is

administered by the Health Resources and Services Administration, requires participating companies to agree to charge statutorily defined covered entities no more than the 340B "ceiling price" for our covered outpatient drugs. The 340B ceiling price is calculated using a statutory formula, which is based on pricing data calculated under the Medicaid Drug Rebate program. The FSS pricing program, which is administered by the Department of Veterans Affairs, or VA, also requires participating companies to extend discounted prices to the VA, Department of Defense, Coast Guard, and Public Health Service. Similar to the 340B program, FSS prices are calculated utilizing pricing data reported by us to the VA on a quarterly and annual basis.

The Medicare Part D program provides a voluntary prescription drug benefit to Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities, which provide coverage of outpatient prescription drugs such as our CF medicines. Unlike Medicare Part A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, including CF, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutics committee. U.S. government payment for some of the costs of prescription drugs may increase demand for products for which we receive marketing approval. However, any negotiated prices for our products covered by a Part D prescription drug plan likely will be lower than the prices we might otherwise obtain.

Private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. As a result, any reduction in payment that results from Part D reimbursement may result in a similar reduction in payments from non-governmental payors for our products. Additionally, private payors, including health maintenance organizations and pharmacy benefit managers in the U.S., are adopting more aggressive utilization management techniques and are increasingly requiring significant discounts and rebates from manufacturers as a condition to including products on formulary with favorable coverage and copayment/coinsurance. As a consequence, these payors may not cover or adequately reimburse for use of our products or may do so at levels that disadvantage them relative to competitive products.

The U.S. government has shown significant interest in implementing cost-containment programs for medicines and has enacted reforms at the state and federal level designed to, among other things, modify prescription drug reimbursement amounts and methodologies, and otherwise control health care costs. For example, the American Recovery and Reinvestment Act of 2009 provided funding for the federal government to compare the effectiveness of different treatments for the same illness. A plan for the research was to be developed by the Department of Health and Human Services, or HHS, the Agency for Healthcare Research and Quality and the National Institutes of Health, or NIH, and periodic reports on the status of the research and related expenditures were to be made to the U.S. Congress. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, it is not clear what effect, if any, the research will have on the sales of our products. In the future, it is possible that comparative effectiveness research demonstrating benefits of a competitor's product could adversely affect the sales of our products. If third-party payors do not consider our products to be cost-effective compared to other available therapies, they may not cover our products as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

The Patient Protection and Affordable Care Act, or ACA, was enacted in March 2010 and was designed to expand coverage for the uninsured while at the same time containing overall health care costs. With regard to pharmaceutical products, among other things, the ACA was designed to expand and increase industry rebates for drugs covered under Medicaid programs, impose an annual fee on branded pharmaceutical manufacturers, subject biological products to potential competition by lower-cost biosimilars, and make changes to the coverage requirements under the Medicare Part D program. We anticipate that the U.S. government will continue to engage in activities seeking to address drug pricing and reimbursement.

In Europe and other foreign jurisdictions, the success of our products depends largely on obtaining and maintaining government reimbursement, because patients are unable to access prescription pharmaceutical products that are not reimbursed by their governments. In some countries, such as Germany, commercial sales of a new product may begin while pricing and reimbursement terms are under discussion. In other countries, a company must complete reimbursement negotiations prior to the commencement of commercial supply of the pharmaceutical product. The requirements governing drug pricing vary widely country-by-country and region-by-region. For example, the member states of the E.U. can restrict the range of drugs for which their national health insurance systems provide reimbursement and can control the prices of

prescription drugs. In addition, many ex-U.S. government payers require companies to provide health economic assessments of products, which are evaluated by government agencies set up for this purpose. A member state may approve a specific price for the drug or it may instead adopt a system of direct or indirect controls on the total amount of money that a company may receive for supply of a drug. Countries also may consider increasing mandatory discounts over time in an attempt to manage increased demands on healthcare budgets. Reimbursement discussions in foreign countries often result in a reimbursement price that is lower than the net price that companies can obtain for the product in the U.S. In addition, reimbursement discussions may take a significant period of time resulting in commercialization delays. Reimbursement for our products cannot be assured because a country or region may only provide for reimbursement on terms that we do not deem adequate.

We have obtained broad reimbursement for our CF medicines in ex-U.S. markets. TRIKAFTA/KAFTRIO is reimbursed or accessible in more than 20 countries outside the U.S. We expect to continue to focus significant resources to obtain expanded reimbursement for our CF medicines and pipeline therapies in ex-U.S. markets.

STRATEGIC TRANSACTIONS AND COLLABORATIONS

As part of our business strategy, we seek to license or acquire products, product candidates, businesses and other technologies that are aligned with our corporate and research and development strategies and complement and advance our ongoing research and development efforts. In addition, we establish business relationships with collaborators to support our research activities and to lead or support development and/or commercialization of certain product candidates. We expect to continue to identify and evaluate potential acquisitions, licenses and collaborations that may be similar or different from the transactions that we have engaged in previously.

Strategic Transactions

Semma Therapeutics

In 2019, we acquired Semma, a privately-held company focused on the use of stem cell-derived human islets as a potentially curative treatment for T1D, for approximately $950.0 million in cash. Our acquisition of Semma advanced our cell therapy capabilities and supports the development of transformative therapies for T1D. We are leveraging this platform to develop cell therapies designed to replace insulin-producing islet cells that are destroyed in people with T1D, with the goal of delivering a potential functional cure.

Exonics Therapeutics

In 2019, we acquired Exonics, a privately held company focused on creating transformative gene-editing therapies to repair mutations that cause DMD and other severe neuromuscular diseases, including DM1. Our acquisition of Exonics enhanced our gene-editing capabilities and supports the potential development of novel therapies for DMD and DM1. In connection with the acquisition, we acquired all of the outstanding equity of Exonics for an upfront payment of approximately $245.0 million plus customary working capital adjustments in cash, and certain potential future payments based primarily upon the successful achievement of specified development and regulatory milestones for the DMD and DM1 programs.

Collaboration and Licensing Arrangements

Joint Development and Commercialization Agreement with CRISPR

In December 2017, we entered into a joint development and commercialization agreement, or Original JDCA, with CRISPR pursuant to which we are co-developing and preparing to co-commercialize CTX001 for TDT and SCD. We entered into the Original JDCA following our exercise of an option to co-develop and co-commercialize the hemoglobinopathies program that was contained in the collaboration agreement that we entered into with CRISPR in 2015.

In April 2021, we and CRISPR amended and restated the Original JDCA, or the A&R JDCA. Pursuant to the A&R JDCA, the parties agreed to, among other things, (a) adjust the governance structure for the collaboration and adjust the responsibilities of each party thereunder; (b) adjust the allocation of net profits and net losses between the parties; and (c) exclusively license (subject to CRISPR's reserved rights to conduct certain activities) certain intellectual property rights to us relating to the products that may be researched, developed, manufactured and commercialized under such agreement.

Pursuant to the A&R JDCA, we lead global development, manufacturing and commercialization of CTX001, with support from CRISPR. Subject to the terms and conditions of the A&R JDCA, we have the right to conduct all research, development, manufacturing and commercialization activities relating to the product candidates and products under the A&R JDCA (including CTX001) throughout the world, subject to CRISPR's reserved right to conduct certain activities.

In connection with the A&R JDCA, we made a $900.0 million upfront payment to CRISPR in the second quarter of 2021. CRISPR has the potential to receive an additional one-time $200.0 million milestone payment upon receipt of the first marketing approval of CTX001 from the FDA or the European Commission.

We and CRISPR shared equally all expenses incurred under the Original JDCA. On July 1, 2021, with respect to CTX001, the net profits and net losses incurred pursuant to the A&R JDCA began to be allocated 60% to us and 40% to CRISPR, while all other product candidates and products continued to have net profits and net losses shared equally between the parties.

Either party may terminate the A&R JDCA upon the other party's material breach, subject to specified notice and cure provisions, or, in our case, in the event that CRISPR becomes subject to specified bankruptcy, winding up, or similar circumstances. Either party may terminate the A&R JDCA in the event the other party commences or participates in any action or proceeding challenging the validity or enforceability of any patent that is licensed to such challenging party pursuant to the A&R JDCA. We also have the right to terminate the A&R JDCA for convenience at any time after giving prior written notice. If circumstances arise pursuant to which a party would have the right to terminate the A&R JDCA on account of an uncured material breach, such party may elect to keep the A&R JDCA in effect and cause such breaching party to be treated as if it had exercised its opt-out rights with respect to the products associated with such uncured material breach and the royalties payable to the breaching party would be reduced by a specified percentage.

Either party may opt out of the development of a product candidate under the A&R JDCA after predetermined points in the development of the product candidate, on a candidate-by-candidate basis. In the event of such opt-out, the party opting-out will no longer share in the net profits and net losses associated with such product candidate and, instead, the opting out party will be entitled to high single to mid-teen percentage royalties on the net sales of such product, if commercialized.

In-License Agreements

We have entered into various agreements pursuant to which we have obtained access to technologies from third parties and are conducting research and development activities with collaborators. Pursuant to these arrangements, we have obtained development and commercialization rights to resulting product candidates. Depending on the terms of the arrangements, we may be responsible for the costs of research activities, required to make upfront payments and/or milestone payments upon the achievement of certain research, development, and commercial objectives, and/or pay royalties on future sales, if any, of commercial products resulting from the collaboration. Our current in-license agreements include:

- Affinia Therapeutics, Inc. In 2020, we entered into a collaboration with Affinia to gain access to a novel library of AAV capsids to support our ongoing research and development efforts in genetic therapies, including DMD, DM1, and CF.
- Arbor Biotechnologies, Inc. In 2018, we entered into a collaboration with Arbor Biotechnologies, or Arbor, pursuant to which we are focusing on the discovery of novel proteins, including DNA endonucleases, to advance the development of new gene-editing therapies. In 2021, we entered into a new collaboration with Arbor to enhance efforts in developing ex vivo engineered cell therapies for multiple serious diseases using Arbor's proprietary CRISPR gene-editing technology.
- CRISPR Therapeutics AG. As described above, in 2015, we entered into a collaboration with CRISPR for the discovery and development of potential new treatments aimed at the underlying genetic causes of human diseases using CRISPR/Cas9 gene-editing technology. We are developing CTX001 for the treatment of SCD and beta thalassemia. In addition, we have exercised options to exclusively license treatments for specific targets, including CF, that were subject to the research program. In 2019, we obtained exclusive worldwide rights to CRISPR's intellectual property for DMD and DM1 gene-editing products through a new agreement with CRISPR.

- Kymera Therapeutics, Inc. In 2019, we entered into a collaboration with Kymera Therapeutics for the research and development of small molecule protein degraders. Under the collaboration, Kymera Therapeutics conducts research activities in multiple targets, and upon designation of a clinical development candidate for a target, we have the option to exclusively license molecules against the target.

- Mammoth Biosciences, Inc. In 2021, we entered into a collaboration with Mammoth Biosciences, or Mammoth, to develop in vivo gene-editing therapies for two diseases using Mammoth's next-generation CRISPR systems.

- Moderna, Inc. In 2016, we entered into a collaboration with Moderna, pursuant to which we are seeking to identify and develop mRNA therapeutics for the treatment of CF. In 2020, we entered into a new collaboration with Moderna aimed at the discovery and development of lipid nanoparticles and mRNAs that can deliver gene-editing therapies to lung cells for the treatment of CF.

- Obsidian Therapeutics, Inc. In 2021, we entered into a collaboration with Obsidian Therapeutics, or Obsidian, aimed at the discovery of novel therapies that regulate gene-editing for the treatment of serious diseases. This collaboration enables us to leverage Obsidian's cytoDRiVE® platform technology to discover gene-editing medicines whose therapeutic activity can be precisely controlled using small molecules.

- Skyhawk Therapeutics, Inc. In 2020, we entered into a collaboration with Skyhawk Therapeutics for the discovery and development of novel small molecules that modulate RNA splicing for the treatment of serious diseases.

- Other Arrangements. In 2019, we entered into a collaboration with Ribometrix, Inc. In 2018, we entered into agreements with Genomics plc, Merck KGaA, Darmstadt, Germany, and X-Chem, Inc. in order to support our research and development efforts.

Out-license Agreements

We have entered into various agreements pursuant to which we have out-licensed rights to certain product candidates to third-party collaborators. Pursuant to these out-license arrangements, our collaborators are responsible for all costs related to the continued development of such product candidates and obtain development and commercialization rights to these product candidates. Depending on the terms of the arrangements, our collaborators may be required to make upfront payments, milestone payments upon the achievement of certain research and development objectives and/or pay royalties on future sales, if any, of commercial products licensed under the agreement. Our current out-license agreements include a Strategic Collaboration and License Agreement with Merck KGaA, Darmstadt, Germany, that we entered into in 2017, pursuant to which we granted an exclusive worldwide license to research, develop and commercialize four oncology research and development programs.

Cystic Fibrosis Foundation Therapeutics Incorporated

In 2004, we entered into a collaboration agreement with the Cystic Fibrosis Foundation, or CFF, as successor in interest to the Cystic Fibrosis Foundation Therapeutics, Inc., to support research and development activities. Pursuant to the collaboration agreement, as amended, we have agreed to pay tiered royalties ranging from single digits to sub-teens on covered compounds first synthesized and/or tested during a research term on or before February 28, 2014, including KALYDECO (ivacaftor), ORKAMBI (lumacaftor in combination with ivacaftor) and SYMDEKO/SYMKEVI (tezacaftor in combination with ivacaftor) and royalties ranging from low-single digits to mid-single digits on potential net sales of certain compounds first synthesized and/or tested between March 1, 2014 and August 31, 2016, including elexacaftor. For combination products, such as ORKAMBI, SYMDEKO/SYMKEVI and TRIKAFTA/KAFTRIO (elexacaftor, tezacaftor, and ivacaftor), sales are allocated equally to each of the active pharmaceutical ingredients in the combination product.

INTELLECTUAL PROPERTY

Patents and other proprietary rights such as trademarks, trade secrets, and copyrights are critical to our business. We actively seek protection for our products and proprietary information by means of U.S. and foreign patents, trademarks, and copyrights, as appropriate. In addition, we rely upon trade secret protection and contractual arrangements to protect certain of our proprietary information and products.

Patents provide a period of exclusivity that can make it more difficult for competitors to market and use our technology.

We own and control patents and pending patent applications that relate to compounds, formulations, treatment of diseases, synthetic routes, intermediates, and other inventions.

To protect our intellectual property, we typically apply for patents several years before a product receives marketing approval. Under current law, a patent expires 20 years from its first effective filing date. Since the drug development process may last for many years, there may be a period of time in which we have an issued patent but not marketing approval to sell the drug. To compensate for patent term lost while a product is in clinical trials and undergoing review for marketing approval, we may be able to apply for patent term extensions or supplementary protection certificates in some countries. In addition to patent protection, we have regulatory exclusivity from U.S. and European regulatory agencies for the active pharmaceutical agents and, where applicable, their approved orphan indications for a certain time period. Regulatory exclusivity runs concurrently with patent exclusivity and provides complementary protection.

We own or hold exclusive and non-exclusive licenses to several hundred patents in the U.S. Upon approval of a New Drug Application, or NDA, or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or a method of using the product. Each of the patents listed by the NDA sponsor is published in the FDA's Orange Book. We have ten issued U.S. patents listed in the Orange Book that cover the active pharmaceutical ingredients in KALYDECO, its marketed formulations, and/or its approved indication. We have 20 issued U.S. patents listed in the Orange Book that cover the active pharmaceutical ingredients in ORKAMBI, its marketed formulations, and/or its approved indication. We have 21 issued U.S. patents listed in the Orange Book that cover the active pharmaceutical ingredients in SYMDEKO, its marketed formulation, and/or its approved indication. We have 22 issued U.S. patents listed in the Orange Book that cover the active pharmaceutical ingredients in TRIKAFTA, its marketed formulation, and/or its approved indication.

The table below sets forth the year of projected expiration for the basic product patents covering each of our approved products. For products that are combinations of two or more active ingredients, the table lists the projected expiration of the latest expiring patent covering any of the active pharmaceutical ingredients (lumacaftor for ORKAMBI, tezacaftor for SYMDEKO/SYMKEVI and elexacaftor for TRIKAFTA/KAFTRIO). Patent term extensions, supplementary protection certificates, and pediatric exclusivity periods are not reflected in the expiration dates listed in the table below and may extend protection. In some instances, we also own later-expiring patents and applications relating to solid forms, formulations, methods of manufacture, or the use of these drugs in the treatment of particular diseases or conditions. In some cases, however, such patents may not protect our drug from generic competition after the expiration of the basic patent.

Product	Projected Expiration of U.S. Patent	Projected Expiration of European Patent
KALYDECO	2027	2025 [1]
ORKAMBI	2030	2026 [2]
SYMDEKO/SYMKEVI	2027	2028 [3]
TRIKAFTA/KAFTRIO	2037	2037

[1] Certain European countries have granted supplementary protection certificates for KALYDECO, which expire in 2027.

[2] Certain European countries have granted supplementary protection certificates for ORKAMBI, which expire in 2030.

[3] Certain European countries have granted supplementary protection certificates for SYMKEVI, which expire in 2033.

In addition to protecting our marketed products, we actively monitor and file patent applications in the U.S. and in foreign countries on inventions relating to our pipeline. For example, we also own and/or control U.S. and foreign patents and/or patent applications relating to the following:

- CTX001 and other potential gene-editing approaches for treating hemoglobinopathies.
- VX-147 and other compounds being studied for the potential treatment of APOL1-mediated kidney disease.
- VX-121, VX-561, and other CF potentiators and correctors and many other related compounds, and the use of those compounds to treat CF.
- VX-548 and other compounds being studied for the potential treatment of pain.
- VX-880 and other cell-based approaches for treating T1D.

- Other pre-clinical and clinical candidates and the use of such candidates to treat specified diseases.
- The manufacture, pharmaceutical compositions, related solid forms, formulations, dosing regimens, and methods of use of many of the above compounds.

We and CRISPR intend to rely upon a combination of rights, including patent rights, trade secret protection, and regulatory exclusivities to protect CTX001. CRISPR has licensed certain rights to a worldwide patent portfolio that covers various aspects of the CRISPR/Cas9 editing platform technology including, for example, compositions of matter and methods of use, including their use in targeting or cutting DNA, from Dr. Emmanuelle Charpentier. In addition to Dr. Charpentier, this patent portfolio has named inventors who assigned their rights to the Regents of the University of California or the University of Vienna, to whom we refer, together with Dr. Charpentier, as the CVC Group. CRISPR has non-exclusive or co-exclusive rights to the patent rights that protect the core CRISPR/Cas9 gene-editing technology. For example, certain third parties, including competitors, have reported obtaining a license to rights in this patent portfolio in certain fields. In addition, patents and patent applications in this patent portfolio are the subject of proceedings in the U.S., Europe, and other jurisdictions, including proceedings in the U.S. Patent and Trademark Office, or USPTO, between the CVC Group and (separately) the Broad Institute, Sigma-Aldrich, Co. LLC, or Sigma-Aldrich, and ToolGen, Inc., or ToolGen. To date, both the CVC Group and the Broad Institute have obtained granted patents that purport to cover aspects of CRISPR/Cas9 editing platform technology. The patents and patent applications within the patent portfolios of the CVC Group, the Broad Institute, Sigma-Aldrich and/or ToolGen are, or may in the future be, involved in proceedings similar to interferences or priority disputes in Europe or other foreign jurisdictions. In addition to the patent portfolio licensed from Dr. Charpentier, we own patent applications relating to the composition, manufacture, and use of CTX001.

From time to time, we enter into exclusive and non-exclusive license agreements for proprietary third-party technology used in connection with our research activities. These license agreements typically provide for the payment by us of a license fee but may also include terms providing for milestone payments or royalties for the development and/or commercialization of our drug products arising from the related research.

We cannot be certain that issued patents we own or license will be enforceable or provide adequate protection or that pending patent applications will result in issued patents. The existence of patents does not guarantee our right to practice the patented technology or commercialize the patented product. Litigation, interferences, oppositions, *inter partes* reviews, administrative challenges or other similar types of proceedings may be necessary in some instances to determine the validity and scope of certain patents, regulatory exclusivities or other proprietary rights, and in other instances to determine the validity, scope or non-infringement of intellectual property rights that may be claimed by third parties to be pertinent to the manufacture, use or sale of our products.

MANUFACTURING

As we market and sell our approved products and advance our product candidates through clinical development toward commercialization, we continue to build and maintain our supply chain and quality assurance resources. We rely on internal capabilities and a global network of third parties to manufacture and distribute our product candidates for clinical trials, as well as our products for commercial sale and post-approval clinical trials. In addition to establishing supply chains for each new approved product, we must adapt our supply chain for existing products to include additional formulations that are often required in order to treat younger patients or to increase scale of production for existing products. We are focused on ensuring the stability of the supply chains for our current products, including TRIKAFTA/KAFTRIO, and for our pipeline programs. In addition, we are focused on identifying and ensuring efficient manufacturing and delivery processes for the cell and genetic therapies we are developing.

We have established our own manufacturing capabilities in Boston, which we use for clinical trial and commercial supplies, including our commercial supply of TRIKAFTA/KAFTRIO, and are evaluating additional manufacturing capacity for our current and future products. We expect that we will continue to rely on third parties to meet our commercial supply needs, including for TRIKAFTA/KAFTRIO, and a significant portion of our clinical supply needs for the foreseeable future.

Our supply chain for sourcing raw materials and manufacturing our products, including obtaining all necessary supplies, is a multi-step global endeavor. In general, these raw materials and other necessary supplies are available from multiple sources. Third-party contract manufacturers, including some in China, perform different parts of our manufacturing process. Contract manufacturers may supply us with raw materials, convert these raw materials into drug substance and/or

convert the drug substance or product into final dosage form. In addition, third parties assist us with packaging, warehousing, and global distribution of our products.

Establishing and managing this global supply chain for each of our products and product candidates requires a significant financial commitment and the creation and maintenance of numerous third-party contractual relationships. In order to manufacture our commercial products, we utilize both continuous manufacturing technology as well as batch manufacturing processes. While continuous process manufacturing has been used in many industries, we believe that we are the first company to obtain FDA approval for a fully-continuous drug product manufacturing process. We have a limited number of critical steps in our manufacturing process that are single sourced, including for recently launched products. To ensure the stability of our supply chains, we continue to develop alternatives for our manufacturing processes.

We have developed systems and processes to track, monitor, and oversee our and our third-party manufacturers' activities, including a quality assurance program intended to ensure that our third-party manufacturers comply with current Good Manufacturing Practices, or cGMP. We devote substantial time, money and effort in the areas of production, quality control, and quality assurance to maintain cGMP compliance. We regularly evaluate the performance of our third-party manufacturers with the objective of confirming their continuing capabilities to meet our needs efficiently and economically. Manufacturing facilities, both foreign and domestic, are subject to inspections by or under the authority of the FDA and other U.S. and foreign government authorities. Although we actively engage with regulatory authorities, the timing of inspections and regulatory approvals for each of these facilities may be delayed for a number of reasons, including the COVID-19 pandemic.

The manufacturing processes for cell and genetic therapies are more complex than those required for small molecule drugs and require different systems, equipment, facilities, and expertise. Additionally, we are unable to utilize a single process for all of our cell and genetic therapies; they must be customized for each program and therapy. We are investing and plan to continue to invest significant resources in expanding and strengthening our manufacturing supplies, infrastructure and capabilities, independently and through third-party networks, in an effort to develop and commercialize our cell and genetic therapies. We are focused on identifying, evaluating and securing relationships with various third parties globally that will enable us to expand and strengthen such capabilities to support our current and future cell and genetic therapy programs, including CTX001.

We rely on third-party manufacturers to produce or process cell culture reagents, gene-editing components, such as Cas9 protein and guide RNA molecules, and to generate gene-edited cells to supply CTX001 for clinical trials. If approved, we expect to continue to rely on third-party manufacturers for commercial supply of CTX001. The manufacturing process for CTX001 involves a number of steps prior to the final infusion of drug product into patients. Following mobilization and collection of blood cells from the patient at the clinical site, cells are transferred to a manufacturing site where HSPCs are purified and CRISPR/Cas9 gene-editing is performed. The edited cellular product, called CTX001, is frozen and transported back to the clinical site where it is stored prior to infusion into the patient. Each step must be completed successfully, and in a timely manner, requiring coordination between us, clinical sites, third-party manufacturers and shipping vendors. To increase production to commercial levels, we are making significant investments to coordinate manufacturing and logistics activities at a larger scale across multiple facilities to serve the geographies in which we plan to seek approval for CTX001. In addition to clinical data establishing the safety and efficacy of CTX001, approval of CTX001 will require regulatory approval of the processes and facilities used to manufacture CTX001.

COMPETITION

The pharmaceutical industry is characterized by extensive research efforts, rapid technological progress, and intense competition. There are many public and private companies, including pharmaceutical companies and biotechnology companies, engaged in developing products for the indications our drugs are approved to treat and the therapeutic areas we are targeting with our research and development activities. Potential competitors also include academic institutions, government agencies, other public and private research organizations and charitable venture philanthropy organizations that conduct research, seek patent protection and/or establish collaborative arrangements for research, development, manufacturing and commercialization. Mergers and acquisitions in the pharmaceutical, biotechnology and gene therapy industries may result in a larger concentration of resources among a smaller number of our competitors. Some of our competitors may have substantially greater financial, technical, marketing and human resources than we do.

We believe that competition in our industry is based on, among other factors, innovative research, the effective and rapid

development of product candidates, the ability to market and obtain reimbursement for products and the ability to establish effective patent protection. We face competition based on the safety and efficacy of our product and product candidates, the timing and scope of regulatory approvals, the availability and cost of supply, marketing and sales capabilities, reimbursement coverage, price, patent protection and other factors. Our competitors may develop or commercialize more effective, safer or more affordable products than we are able to develop or commercialize or obtain more effective patent protection. As a result, our competitors may commercialize products more rapidly or effectively than we do, which would adversely affect our competitive position, the likelihood that our product candidates, if approved, would achieve and maintain market acceptance and our ability to generate meaningful revenues from our products. Future competitive products may render our products, or future products, obsolete or noncompetitive. Another key element of remaining competitive in our industry is recruiting and retaining leading scientific, technical and management personnel to conduct our research activities and advance our development programs, including with the commercial expertise to effectively market our products.

Cystic Fibrosis

A number of companies are seeking to identify and develop product candidates for the treatment of CF, including CFTR modulators and other therapies intended to address the underlying causes of CF.

AbbVie, Inc., or AbbVie, has indicated that it plans to develop a triple combination CFTR modulator therapy comprised of a potentiator and correctors. AbbVie has been conducting a dose-ranging study of a potentiator and corrector and a separate proof of concept study for a combination of their potentiator and correctors, and is expected to announce data in 2022. Proteostasis Therapeutics, Inc. was developing potential CFTR modulator therapies prior to its acquisition by Yumanity Therapeutics, Inc., or Yumanity. Following the merger, Yumanity out-licensed the CF program.

Other therapeutic approaches include addressing CF utilizing nucleic acid therapies and read-through agents, which are compounds that allow expression of a full-length protein. Nucleic acid therapies are under development by companies such as Arcturus Therapeutics Holdings, Inc., ReCode Therapeutics, Inc., Krystal Biotech, Inc., Spirovant Sciences, Inc. and 4D Molecular Therapeutics, Inc. Eloxx Pharmaceuticals, Inc. is evaluating a read-through therapy for nonsense CFTR mutations in two Phase 2 clinical trials and is planning additional trials to evaluate this therapy in combination with CFTR modulators.

Our success in rapidly developing and commercializing our products may increase the resources that our competitors allocate to the development of these potential treatments for CF. In addition, clinical trials conducted by our competitors could take place simultaneously with our own trials, and may slow down our pace of development if we are unable to recruit sufficient clinical trial subjects. If one or more competing therapies are successfully developed as a treatment for people with CF, our revenues from our current products and/or additional CF products, if then approved, could face significant competitive pressure.

Pipeline

In recent years, we have committed significant research resources to, and made significant investments in, our pipeline of potential new therapies for SCD, TDT, AMKD, T1D, pain, AATD, muscular dystrophies, and other diseases.

Sickle Cell and Beta Thalassemia

There are multiple approved treatments for SCD and beta thalassemia, including products from Novartis International AG, or Novartis, Global Blood Therapeutics, Inc. and Bristol Myers Squibb together with Acceleron Pharma, Inc., recently acquired by Merck & Co. In addition, Bluebird Bio, Inc., or Bluebird, has a gene therapy, Zynteglo (betibeglogene autotemcel) that has a conditional marketing authorization from the EMA for the treatment of certain beta thalassemia genotypes and is under FDA review in the U.S. Bluebird has indicated it anticipates withdrawing marketing authorizations for Zynteglo from both the E.U. and U.K. by early 2022. Bluebird is also developing a gene therapy program for SCD. In addition, various companies and private academic/medical institutes are developing gene therapy or gene-editing candidates for the treatment of SCD or beta thalassemia utilizing CRISPR technology, lenti-viral vectors, zinc finger nuclease technology, or base editing.

Additional Programs

Certain of our other product candidates face competition from many pharmaceutical and biotechnology companies. For example, we are aware of other pharmaceutical and biotechnology companies actively engaged in the research and development of products for T1D, including insulin injections, pumps, and hybrid closed loop systems. People living with

T1D have had access to insulin as a treatment option for a century, providing for a very well entrenched standard of care. Several other companies are investing in additional approaches as a potential treatment for T1D including dual-hormonal closed loop systems, cell and gene therapies, and immunotherapies.

In acute pain, the market is dominated by conventional analgesics (e.g., opioids, non-steroidal anti-inflammatory drugs, acetaminophen and local anesthetics), low-cost generics, and reformulations aiming to provide safer, more tolerable and/or more convenient therapies. However, several companies are pursuing clinical development on novel mechanisms of action for pain indications, including some that are in early stages, targeting the sodium channels in the NaV family.

Many other pharmaceutical and biotechnology companies are investing resources for the discovery and development of small molecules and cell and gene therapies to treat the same disease areas for which we are developing therapies in our pipeline. If any of these competitors develop or successfully commercialize products involving therapies competitive with our pipeline therapies, the potential return on our investment in those pipeline therapies could be impacted.

GOVERNMENT REGULATION

Our operations and activities are subject to extensive regulation by numerous government authorities in the U.S., the E.U. and other countries. In the U.S., the E.U. and other countries, our products are subject to rigorous regulations governing their testing, manufacture, labeling, storage, record keeping, approval, and advertising and promotion. As a result of these regulations, product development and product approval processes are very expensive and time consuming. The regulatory requirements applicable to drug and biologic development, approval, and marketing are subject to change. In addition, regulations and administrative guidance often are revised or reinterpreted by the agencies in ways that may significantly affect our business and our products. It is impossible to predict whether legislative changes will be enacted, or FDA or comparable ex-U.S. regulations, guidance or interpretations will change.

United States Government Regulation

New Drug Application and Biologics License Application Approval Processes

The process required by the FDA before a drug or biologic may be marketed in the U.S. generally involves the following:

- completion of preclinical laboratory tests, animal studies and formulation studies conducted according to Good Laboratory Practices, or GLP, and other applicable regulations;
- submission to the FDA of an IND, which must become effective before clinical trials in the U.S. may begin;
- performance of adequate and well-controlled clinical trials according to Good Clinical Practices, or GCP, and other clinical trial-related regulations to establish the safety and efficacy of the proposed drug for its intended use;
- submission to the FDA of an NDA or a Biologics License Application, or BLA;
- satisfactory completion of a pre-approval FDA inspection of the manufacturing facility or facilities at which the product will be produced to assess compliance with cGMP; and
- FDA review and approval of the NDA or BLA.

Once a drug or biologic is identified for development, it enters the preclinical testing stage. Preclinical tests include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal pharmacology and toxicology studies. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information and analytical data, to the FDA as part of the IND, which seeks FDA approval to test the drug or biologic in humans. Preclinical or nonclinical testing typically continues even after the IND is submitted.

If the FDA accepts the IND, the drug or biologic can then be studied in human clinical trials to determine if the product candidate is safe and effective. Clinical trials involve three separate phases that often overlap, can take many years and are expensive. These three phases, which are subject to considerable regulation, are as follows:

- *Phase 1.* The drug or biologic initially is introduced into a limited number of healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution and elimination. In the case of some drugs or biologics for severe or life-threatening diseases, such as cancer, especially when the drug or biologic may be inherently too toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.

- *Phase 2.* Clinical trials are next initiated in a limited patient population with the specified disease or condition the drug or biologic is intended to treat in order to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the drug or biologic candidate for the disease or condition it is intended to treat and to determine dosage tolerance and optimal dosage.

- *Phase 3.* Clinical trials are undertaken to further evaluate dosage, clinical efficacy and safety in an expanded patient population at geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk-benefit ratio of the drug or biologic and provide an adequate basis for regulatory approval and product labeling.

It is possible that Phase 1, Phase 2 and Phase 3 testing may not be completed successfully within any specified period, if at all. The FDA or the sponsor may, at any time during the initial 30-day IND review period or while clinical trials are ongoing under the IND, impose a partial or complete clinical hold or suspend a clinical trial at any time for a variety of reasons, including a finding that the healthy volunteers or patients are being exposed to an unacceptable health risk. Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently in other situations, and the occurrence of serious adverse events must also be reported. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health for public dissemination on the *www.clinicaltrials.gov* website.

Post-approval trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication and are commonly intended to generate additional safety data regarding use of the product in a clinical setting. In certain instances, the FDA may mandate the performance of Phase 4 clinical trials as a condition of approval of an NDA or BLA.

The results of drug or biologic development, preclinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests conducted on the chemistry of the drug or biologic, proposed labeling and other relevant information are submitted to the FDA as part of an NDA or BLA requesting approval to market the drug or biologic. The FDA reviews each NDA or BLA submitted to ensure that it is sufficiently complete for substantive review before it accepts it for filing. It may request additional information rather than accept an NDA or BLA for filing.

Once the submission is accepted for filing, the FDA begins an in-depth review. The FDA reviews an NDA or BLA to determine, among other things, whether a drug or biologic is safe and effective for its intended use and whether its manufacturing is cGMP-compliant to assure and preserve the drug or biologic's identity, strength, quality and purity. The FDA may refer the NDA or BLA to an advisory committee for review and recommendation as to whether the NDA or BLA should be approved and under what conditions. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations. Before approving an NDA or BLA, the FDA will inspect the facility or facilities where the drug or biologic is manufactured and tested. Additionally, before approving an NDA or BLA, the FDA may inspect one or more clinical trial sites to assure compliance with GCP requirements.

The FDA may require, as a condition of approval, restricted distribution and use, enhanced labeling, special packaging or labeling, expedited reporting of certain adverse events, pre-approval of promotional materials, restrictions on direct-to-consumer advertising or commitments to conduct additional research post-approval. The FDA will issue a complete response letter if the agency decides not to approve the NDA or BLA in its present form.

Expedited Review and Approval

The FDA has developed a number of distinct approaches to make new drugs or biologics available as rapidly as possible in cases where there is no available treatment or there are advantages over existing treatments.

The FDA may grant "accelerated approval" to products that have been studied for their safety and effectiveness in treating serious illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. For accelerated approval, the product must have an effect on a surrogate endpoint or an intermediate clinical endpoint that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on irreversible morbidity and mortality. When

approval is based on surrogate endpoints or clinical endpoints other than survival or morbidity, the sponsor will be required to conduct additional post-approval clinical studies to verify and describe the clinical benefit. These studies are known as "confirmatory trials." Approval of a drug may be withdrawn, or the labeled indication of the drug changed if these trials fail to verify clinical benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the drug or biologic.

The FDA may grant "fast track" status to products that treat serious diseases or conditions and demonstrate the potential to address an unmet medical need. Fast track is a process designed to facilitate the development and expedite the review of such products by providing, among other things, more frequent meetings with the FDA to discuss the product's development plan and rolling review, which allows submission of individually completed sections of an NDA or BLA for FDA review before the entire submission is completed. Fast track status does not ensure that a product will be developed more quickly or receive FDA approval.

"Breakthrough Therapy" designation is a process designed to expedite the development and review of drugs or biologics that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug or biologic may demonstrate substantial improvement over available therapy on one or more clinically significant endpoints. Breakthrough Therapy designation provides all of the benefits of fast track designation in addition to robust FDA-sponsor interaction and communication to help to identify the most efficient and expeditious path for clinical development while minimizing the number of patients placed in ineffective control regimens.

"Regenerative Medicine Advanced Therapy," or RMAT, designation is a process created by the 21st Century Cures Act in December 2016. A product is eligible for RMAT designation if it is a regenerative medicine therapy that is intended to treat, modify, reverse or cure a serious disease or condition, and if preliminary clinical evidence indicates that the product has the potential to address unmet medical needs for such disease or condition. The benefits of RMAT designation include the benefits available to breakthrough therapies, including potential eligibility for priority review and accelerated approval based on surrogate or intermediate endpoints.

The FDA may grant "priority review" status to a product that, if approved, would provide significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions. Priority review is intended to reduce the time it takes for the FDA to review an NDA or BLA, with the goal to take action on the application within six months from when the application is filed, compared to ten months for a standard review.

Manufacturing Quality Control

Among the conditions for NDA or BLA approval is the requirement that the prospective manufacturer's quality control and manufacturing procedures continually conform with cGMP. Manufacturers must devote substantial time, money and effort in the areas of production, quality control, and quality assurance to maintain cGMP compliance. Material changes in manufacturing equipment, location, or process, may result in additional regulatory review and approval. The FDA, and other regulatory agencies, conduct periodic visits to inspect equipment, facilities, and processes following the initial approval of a product. If a manufacturing facility is not in substantial compliance with the applicable regulations and requirements imposed when the product was approved, regulatory or judicial enforcement action may be initiated, which may include a warning letter, suspension of manufacturing, product seizure, or an injunction against shipment of products from the facility and/or recall of products previously shipped. We rely, and expect to continue to rely, on third parties for the production of our products. Future FDA, state, and foreign inspections may identify compliance issues at the facilities of our contract manufacturers that may disrupt manufacture or distribution of our products or require substantial resources to correct.

Post-approval Requirements

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product may result in restrictions on the product or complete withdrawal of the product from the market. In addition, under the FDCA the sponsor of an approved drug in the U.S. may not promote that drug for unapproved, or off-label, uses, although a physician may prescribe a drug for an off-label use in accordance with the practice of medicine. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. Further, after approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further FDA review and approval. In addition, the FDA may require testing, including Phase 4 trials, and surveillance programs to monitor the effect of approved products that have been commercialized, and the FDA has the

power to prevent or limit further marketing of a product based on the results of these post-marketing programs.

Products we manufacture or distribute pursuant to FDA approvals are subject to continuing regulation by the FDA, including, among other things:

- record-keeping requirements;
- reporting of adverse experiences with the product;
- providing the FDA with updated safety and efficacy information;
- drug sampling and distribution requirements;
- notifying the FDA and gaining its approval of specified manufacturing or labeling changes;
- complying with certain electronic records and signature requirements; and
- complying with FDA promotion and advertising requirements.

Failure to comply with the applicable U.S. requirements at any time during the drug or biologic development process, approval process or after approval, may subject us or our collaborators to administrative or judicial sanctions, any of which could have a material adverse effect on us. These sanctions could include:

- restrictions on marketing or manufacturing of the product;
- safety alerts, Dear Healthcare Provider letters, press releases, or other communications containing warnings or other safety information about the product;
- refusal to approve or delay in review of pending applications;
- withdrawal of an approval or the implementation of limitations on a previously approved indication for use;
- imposition of a clinical hold, a risk mitigation and evaluation strategy, or REMS, or other safety-related limitations;
- warning letters or “untitled letters”;
- product seizures, recalls, or detentions, or refusal to permit the import or export of products;
- total or partial suspension of production or distribution;
- consent decrees, corporate integrity agreements, debarment or exclusion from federal healthcare programs; or
- injunctions, fines, disgorgement, refusals of government contracts, or civil or criminal penalties.

United States Patent Term Restoration and Regulatory Exclusivity

Upon approval, products may be entitled to certain kinds of exclusivity under applicable intellectual property and regulatory regimes. The Drug Price Competition and Patent Term Restoration Act of 1984 (commonly known as the Hatch-Waxman Act) permits a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. The length of the patent extension is roughly based on 50 percent of the period of time from the filing of an IND for a compound to the submission of the NDA for such compound, plus 100 percent of the time period from NDA submission to regulatory approval. The extension, however, cannot exceed five years and the patent term remaining after regulatory approval cannot exceed 14 years.

If the FDA approves a drug product that contains a new chemical entity not previously approved, the product is typically entitled to five years of non-patent regulatory exclusivity. Other products may be entitled to three years of exclusivity if approval was based on the FDA’s reliance on new clinical studies essential to approval submitted by the NDA applicant.

Biologics are also entitled to exclusivity under the Biologics Price Competition and Innovation Act, or the BPCIA, which was passed as Title VII to the ACA. The law provides a pathway for approval of products that are biosimilar to or interchangeable with an FDA-licensed reference biological product. Under the BPCIA, a reference biological product is

granted 12 years of data exclusivity, the period of time during which an innovator's clinical data cannot be used by other companies, from the time of first licensure of the product, and an application for a biosimilar product may not be submitted to the FDA until four years following the date that the reference product was first licensed by the FDA. In addition, the approval of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first licensed. The BPCIA also created certain exclusivity periods for biosimilars approved as interchangeable products. At this juncture, it is unclear whether products deemed "interchangeable" by the FDA will, in fact, be readily substituted by pharmacies, which are governed by state pharmacy law. Biologics are also eligible for orphan drug exclusivity, as discussed below. The law also includes an extensive process for the innovator biologic and biosimilar manufacturer to litigate patent infringement, validity, and enforceability prior to the approval of the biosimilar. There have been ongoing federal legislative and administrative efforts as well as judicial challenges seeking to repeal, modify or invalidate some or all of the provisions of the ACA. While none of those efforts have focused on changes to the provisions of the ACA related to the biosimilar regulatory framework, if the ACA is repealed, substantially modified, or invalidated, it is unclear what, if any, impact such action would have on biosimilar regulation.

If the NDA or BLA applicant studies the product for use by children, the FDA may grant pediatric exclusivity, which extends by 180 days each existing exclusivity (patent and regulatory) related to the product.

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs or biologics intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 people in the U.S.

If a drug or biologic that has orphan drug designation subsequently receives the first FDA approval for that drug or biologic for the disease for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications to market the same drug for the same indication for seven years following marketing approval, except in certain very limited circumstances, such as if the later product is shown to be clinically superior to the orphan product. Orphan drug exclusivity, however, also could block the approval of our drugs or biologics for seven years if a competitor first obtains approval of the same product as defined by the FDA or if our drug or biologic is determined to be contained within the competitor's product for the same indication or disease. KALYDECO, ORKAMBI, SYMDEKO, and TRIKAFTA have been granted orphan drug exclusivity by the FDA.

Foreign Regulation

We conduct clinical trials and market our products in numerous jurisdictions outside the U.S. Most of these jurisdictions have clinical trial, product approval and post-approval regulatory processes that are similar in principle to those in the U.S. Thus, whether or not we obtain FDA approval for a product candidate, we must obtain approval by the comparable regulatory authorities of foreign countries or economic areas, such as the E.U., before we can commence clinical trials or market products in those countries or areas. The approval process and requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from place to place, and the time may be longer or shorter than that required for FDA approval.

Under the E.U. regulatory system, a company may submit marketing authorization applications either under a centralized or decentralized procedure. The centralized procedure, which is compulsory for orphan medicines, medicines produced by biotechnology, and those medicines intended to treat AIDS, cancer, neurodegenerative disorders, or diabetes, and optional for those medicines that are highly innovative, provides for the grant of a single marketing authorization that is valid for all E.U. member states. In addition to the centralized procedure, the E.U. also has a nationalized procedure, which requires a separate application to and approval determination by each country; a decentralized procedure, whereby applicants submit identical applications to several countries and receive simultaneous approval; and a mutual recognition procedure, where applicants submit an application to one country for review and other countries may accept or reject the initial decision.

Other Regulations

Pharmaceutical companies are also subject to various laws pertaining to healthcare "fraud and abuse," including the federal Anti-Kickback Statute, or AKS, the False Claims Act, or FCA, and other state and federal laws and regulations. In the U.S., the Anti-Kickback Statute generally makes it illegal to knowingly and willfully solicit, offer, receive or pay any remuneration in return for or to induce the referral of business, including the purchase or prescription of a particular drug that is reimbursed by a state or federal health care program. The FCA prohibits knowingly and willingly presenting, or causing to

be presented for payment to third-party payors (including Medicare and Medicaid), any claims for reimbursed drugs or services that are false or fraudulent, claims for items or services not provided as claimed or claims for medically unnecessary items or services. Violations of fraud and abuse laws may be punishable by criminal and/or civil sanctions, including fines and civil monetary penalties, as well as by the possibility of exclusion from federal healthcare programs (including Medicare and Medicaid). Liability under the FCA may also arise when a violation of certain laws or regulations related to the underlying products (e.g., violations regarding improper promotional activity, manufacturing regulations, or unlawful payments) contributes to the submission of a false claim. If we were subject to allegations concerning, or convicted of violating, these laws, our business could be harmed.

Laws and regulations also have been enacted by the federal government and various states to regulate the sales and marketing practices of pharmaceutical manufacturers. The laws and regulations generally limit financial interactions between manufacturers and health care providers, require manufacturers to adopt certain compliance standards or require disclosure to the government and public of such interactions. The laws include U.S. federal and state "sunshine" provisions. The federal sunshine provisions apply to pharmaceutical manufacturers with products reimbursed under certain government programs and require those manufacturers to disclose annually to the federal government (for re-disclosure to the public) certain payments and other transfers of value made to physicians and teaching hospitals and, beginning with disclosures in 2022, to certain non-physician practitioners. State laws may also require disclosure of pharmaceutical pricing information and marketing expenditures. Many of these laws and regulations contain requirements that are subject to interpretation. Outside the U.S., other countries have implemented requirements for disclosure of financial interactions with healthcare providers and additional countries may consider or implement such laws.

We are subject to various federal and foreign laws that govern our international business practices with respect to payments to government officials. Those laws include the U.S. Foreign Corrupt Practices Act, or FCPA, which prohibits U.S. companies and their representatives from paying, offering to pay, promising, or authorizing the payment of anything of value to any foreign government official, government staff member, political party, or political candidate for the purpose of obtaining or retaining business or to otherwise obtain favorable treatment or influence a person working in an official capacity. In many countries, the health care professionals we regularly interact with may meet the FCPA's definition of a foreign government official. We are also subject to U.K. Bribery Act 2010, or the Bribery Act, which proscribes giving and receiving bribes in the public and private sectors, bribing a foreign public official, and failing to have adequate procedures to prevent employees and other agents from giving bribes. U.S. companies that conduct business in the U.K. generally will be subject to the Bribery Act.

We are subject to federal laws, including the Medicaid Drug Rebate Program, the 340 program, and the FSS pricing program, that require pharmaceutical manufacturers to report certain calculated product prices to the government or provide certain discounts or rebates to government authorities or private entities, often as a condition of reimbursement under government healthcare programs.

Our collection and use of personal data as part of our business activities is subject to various privacy and data security laws and regulations, including oversight by various regulatory or other governmental bodies, in the U.S., E.U., U.K., Canada, Australia, Brazil and other jurisdictions. Such laws and regulations have the potential to affect our business materially, continue to evolve and increasingly are being enforced.

Our present and future business has been and will continue to be subject to various other laws and regulations. Various laws, regulations, and recommendations relating to safe working conditions, laboratory practices, the experimental use of animals, and the purchase, storage, movement, import, export and use and disposal of hazardous or potentially hazardous substances are or may be applicable to our activities. In addition, as we expand our pipeline and contemplate different approaches that may incorporate the use of medical devices, such approaches may necessitate compliance with regulatory laws applicable to medical devices, including those governing the testing, manufacture, approval, distribution, and marketing of medical devices. Furthermore, the extent of government regulation, which might result from future legislation or administrative action, cannot accurately be predicted.

We have a global corporate compliance program designed to actively identify, prevent, and mitigate healthcare fraud and abuse risk through, among other things, the implementation of compliance policies and systems and through the promotion of a culture of compliance. We will continue to devote substantial resources to enhance and expand our corporate compliance program as necessary to help us manage and mitigate our evolving compliance risk environment as our business grows and expands globally. Even with these measures, however, we cannot guarantee compliance with the various complex laws and regulations to which we are subject now or in the future.

EMPLOYEES AND HUMAN CAPITAL MANAGEMENT

As of December 31, 2021, we had approximately 3,900 employees. Of these employees, approximately 3,100 were based in the U.S. and approximately 800 were based outside the U.S. None of our U.S. employees are covered by a collective bargaining agreement. A small number of employees outside the U.S. are covered by such agreements due to local law or industry requirements. We consider our relations with our employees to be good. We face intense competition for our personnel from our competitors and other companies throughout our industry and from universities and research institutions. Over the last several years, the challenges in recruiting and retaining employees across the biotechnology industry have increased substantially due to current industry job market dynamics.

We rely on skilled, experienced, and innovative employees to conduct the operations of our company. The biotechnology industry is very competitive, and recruiting and retaining such employees is important to the continued success of our business. We are committed to building an outstanding, committed, and passionate team at Vertex, and we focus on a culture that values inclusion, diversity, and equity. We believe that each employee brings unique perspectives and strengths, and by embracing these strengths, we can do our best work for patients. We focus on recruiting, retaining, and developing employees from a diverse range of backgrounds to conduct our research, development, commercial, and other business activities.

Our commitment to inclusion, diversity, and equity begins with our executive management team: five of the ten members are women and/or from diverse ethnic and racial minorities. On our Board of Directors, four of our ten members (40%) are women and four members (40%) are ethnic and racial minorities. As of December 31, 2021, women represented 54% of our global workforce and 41% of our leadership (VP and above). As of December 31, 2021, 36% of our U.S. workforce, and 19% of our U.S. leadership (VP and above), were ethnic and racial minorities.

Our inclusion, diversity, and equity strategy and efforts are led by a Vice President in Human Resources. Our initiatives include learning, resources, and forums that activate inclusion, diversity, and equity in our workplaces; efforts to develop a diverse pipeline of talent from early career through leadership; four global employee resource networks that promote connectivity and collaboration across levels and functions, and engage colleagues in personal and professional development opportunities, including mentoring, community outreach, and cultural awareness activities; and investments to fight racism and social injustice.

To promote our employees' continued well-being and development, we offer a variety of inclusive benefits and opportunities. We offer comprehensive work-life benefits, including health, dental, and income protection, such as life insurance and retirement savings programs. In 2021, we continued to enhance and expand our employee benefits in response to the COVID-19 pandemic. For example, we increased company-wide personal time off, provided resources to enable employees to work from home, continued to promote and expand mental wellness tools, and enhanced child/elder care benefits for all employees. We continually review and augment our programs to include benefits such as expanded parental bonding and increased support for family planning. We have also expanded our gender affirming benefits. Our management has continued to assess and respond to the evolving needs of our workforce throughout the pandemic.

In addition, we provide our employees with career development and advancement opportunities, including job rotations, mentoring, and managerial training. We also are committed to identifying and developing our next generation leaders and have developed programs focused on talent and succession for critical roles in our organization.

OTHER MATTERS

Financial Information and Significant Customers

We operate in one segment, pharmaceuticals. Financial information about our revenue by product and significant customers is set forth in Note Q, "Segment Information," to our consolidated financial statements included in this Annual Report on Form 10-K.

Information Available on the Internet

Our internet address is *www.vrtx.com.* Our annual reports on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K, and all amendments to those reports, are available to you free of charge through the "Investors-SEC Filings" section of our website as soon as reasonably practicable after those materials have been electronically filed with, or furnished to, the Securities and Exchange Commission.

Corporate Information

Vertex was incorporated in Massachusetts in 1989, and our principal executive offices are located at 50 Northern Avenue Boston, Massachusetts 02210.

INFORMATION ABOUT OUR EXECUTIVE OFFICERS

The names, ages and positions held by our executive officers are as follows:

Name	Age	Position
Reshma Kewalramani, M.D.	49	Chief Executive Officer and President
Jeffrey M. Leiden, M.D., Ph.D.	66	Executive Chairman
David Altshuler, M.D., Ph.D.	57	Executive Vice President, Global Research and Chief Scientific Officer
Stuart A. Arbuckle	56	Executive Vice President and Chief Operating Officer
Carmen Bozic, M.D.	59	Executive Vice President, Global Medicines Development and Medical Affairs, and Chief Medical Officer
Joy Liu, J.D.	44	Senior Vice President, General Counsel
Amit K. Sachdev, J.D.	54	Executive Vice President, Chief Patient Officer
Bastiano Sanna, Ph.D.	47	Executive Vice President, Chief of Cell and Genetic Therapies
Ourania "Nia" Tatsis, Ph.D.	52	Executive Vice President and Chief Regulatory and Quality Officer
Charles F. Wagner, Jr.	53	Executive Vice President and Chief Financial Officer
Kristen C. Ambrose	45	Senior Vice President and Chief Accounting Officer

Dr. Kewalramani has been our Chief Executive Officer and President since April 2020 and a member of our Board of Directors since February 2020. Dr. Kewalramani was our Executive Vice President and Chief Medical Officer from April 2018 through April 2020. She was our Senior Vice President, Late Development from February 2017 until April 2018. From August 2004 to January 2017, she served in roles of increasing responsibility at Amgen Inc., most recently as Vice President, Global Clinical Development, Nephrology & Metabolic Therapeutic Area and as Vice President, U.S. Medical Organization. From 2014 through 2019, Dr. Kewalramani was the industry representative to the FDA's Endocrine and Metabolic Drug Advisory Committee. Dr. Kewalramani also has served on the board of Ginkgo Bioworks since September 2021. She completed her internship and residency in Internal Medicine at the Massachusetts General Hospital and her fellowship in Nephrology at the Massachusetts General Hospital and Brigham and Women's Hospital combined program. Dr. Kewalramani holds a B.A. from Boston University and an M.D. from Boston University School of Medicine. Dr. Kewalramani also completed the General Management Program at Harvard Business School and is an alumnus of the school.

Dr. Leiden is our Executive Chairman, a position he has held since in April 2020. He was our Chief Executive Officer and President from 2012 through March 2020. He has been a member of our Board of Directors since July 2009, the Chairman of our Board of Directors since May 2012, and served as our lead independent director from October 2010 through December 2011. Dr. Leiden was a Managing Director at Clarus Ventures, a life sciences venture capital firm, from 2006 through January 2012. Dr. Leiden was President and Chief Operating Officer of Abbott Laboratories, Pharmaceuticals Products Group, and a member of the Board of Directors of Abbott Laboratories from 2001 to 2006. From 1987 to 2000, Dr. Leiden held several academic appointments, including the Rawson Professor of Medicine and Pathology and Chief of Cardiology and Director of the Cardiovascular Research Institute at the University of Chicago, the Elkan R. Blout Professor of Biological Sciences at the Harvard School of Public Health, and Professor of Medicine at Harvard Medical School. He is an elected member of both the American Academy of Arts and Sciences and the Institute of Medicine of the National Academy of Sciences. Dr. Leiden is the Chairman of Revolution Healthcare Acquisition Corp., a special purpose acquisition corporation, and a director of the Massachusetts Mutual Life Insurance Company, an insurance company. Dr. Leiden was a

director and the non-executive Vice Chairman of the board of Shire plc, a specialty biopharmaceutical company, from 2006 to January 2012 and a director of Quest Diagnostics, a medical diagnostics company, from December 2014 to May 2019. Dr. Leiden received his M.D., Ph.D. and B.A. degrees from the University of Chicago.

Dr. Altshuler has been our Executive Vice President, Global Research and Chief Scientific Officer since January 2015 and was a member of our Board of Directors from May 2012 through December 2014. Dr. Altshuler was one of four founding members of the Broad Institute, a research collaboration of Harvard University and the Massachusetts Institute of Technology, The Whitehead Institute and the Harvard Hospitals. He served as the Director of the Institute's Program in Medical and Population Genetics from 2003 through December 2014 and as the Institute's Deputy Director and Chief Academic Officer from 2009 through December 2014. Dr. Altshuler joined the faculty at Harvard Medical School and the Massachusetts General Hospital in 2000 and held the academic rank of Professor of Genetics and Medicine from 2008 through December 2014. He served as Adjunct Professor of Biology at MIT from 2012 through December 2014. Dr. Altshuler earned a B.S. from MIT, a Ph.D. from Harvard University and an M.D. from Harvard Medical School. Dr. Altshuler completed his clinical training in Internal Medicine, and in Endocrinology, Diabetes and Metabolism, at the Massachusetts General Hospital.

Mr. Arbuckle is our Executive Vice President, Chief Operating Officer, a position he has held since July 2021. Previously, Mr. Arbuckle served as Executive Vice President, Chief Commercial and Operations Officer from March 2021 to July 2021, and as our Executive Vice President, Chief Commercial Officer from September 2012 to February 2021. Prior to joining us, Mr. Arbuckle held multiple commercial leadership roles at Amgen, Inc. from July 2004 through August 2012. Mr. Arbuckle has worked in the biopharmaceuticals industry since 1986, including more than 15 years at GlaxoSmithKline plc, where he held sales and marketing roles of increasing responsibility for medicines aimed at treating respiratory, metabolic, musculoskeletal, cardiovascular and other diseases. He served as a member of the Board of Directors of Cerulean Pharma, Inc. from June 2015 through July 2017 and has served as a member of the Board of Directors of ImmunoGen, Inc. since January 2018 and of Rhythm Pharmaceuticals Inc. since July 2019. Mr. Arbuckle holds a BSc in Pharmacology and Physiology from the University of Leeds.

Dr. Bozic is our Executive Vice President, Global Medicines Development and Medical Affairs, a position she has held since October 2019, and she has been our Chief Medical Officer since April 2020. She was our Senior Vice President and Head of Global Clinical Development from May 2019 to October 2019. Prior to joining Vertex, Dr. Bozic spent more than 20 years at Biogen Inc., a biotechnology company focused on neurological diseases, most recently as Senior Vice President of Global Development and Portfolio Transformation from 2015 to May 2019 and as Senior Vice President of Clinical and Safety Sciences from 2013 to 2015. Dr. Bozic has served as the industry representative to the FDA's Risk Communication Advisory Committee, and was a member of PhRMA's Clinical and Preclinical Development Committee and the Board of Managers at BioMotiv. She is a member of the Clinical Advisory Board at Akili Interactive. She received her M.D., C.M., completed her residency, and was Chief Resident in Internal Medicine at McGill University. She completed her fellowship in Pulmonary and Critical Care Medicine at Brigham and Women's Hospital, and was an Associate Physician at Beth Israel Deaconess Medical Center and Harvard Medical School before joining the biopharmaceutical industry.

Ms. Liu is our Senior Vice President, General Counsel, a position she has held since March 2021. Previously, Ms. Liu was our Senior Vice President and Deputy General Counsel from February 2020 to February 2021, and our Vice President and Deputy General Counsel from October 2019 to February 2020. Ms. Liu first joined Vertex as our Vice President, Commercial and Regulatory Legal in August 2016. Prior to Vertex, Ms. Liu was an attorney at Ropes & Gray LLP, for 14 years, the last five as a partner. Ms. Liu received her bachelor's degree from Harvard University and her J.D. from Columbia Law School.

Mr. Sachdev is our Executive Vice President, Chief Patient Officer, a role he has held since October 2019. In addition, Mr. Sachdev has served in the role of Chief of Staff to the CEO since April 2020. He served as our Executive Vice President and Chief Regulatory Officer from January 2017 until September 2019, and as our Executive Vice President, Policy, Access and Value from October 2014 through December 2016. In 2010, he established our first international commercial operations in Canada. In 2007, he joined us as a Senior Vice President, and has led our government affairs and public policy activities, as well as our patient advocacy programs. Prior to joining us, Mr. Sachdev served as Executive Vice President, Health, of the Biotechnology Industry Organization (BIO) and was the Deputy Commissioner for Policy at the FDA, where he also served in several other senior positions. Prior to the FDA, Mr. Sachdev served as Majority Counsel to the Committee on Energy and Commerce in the U.S. House of Representatives and practiced law at the American Chemistry Council, and subsequently at the law firm of Ropes & Gray LLP. He has served as a member of the Board of Directors of Eiger BioPharmaceuticals since

April 2019. Mr. Sachdev holds a B.S from Carnegie Mellon University and a J.D. from Emory University School of Law.

Dr. Sanna is our Executive Vice President, Chief of Cell and Genetic Therapies, a position he has held since February 2020. From October 2019 to February 2020, he was President of Semma Therapeutics, Inc., a private biotechnology company that Vertex acquired in October 2019. Prior to the acquisition, Dr. Sanna was the Chief Executive Officer and President of Semma from May 2018 until October 2019. Dr. Sanna was Chief Operating Officer at Magenta Therapeutics from May 2016 through April 2018. He served on the leadership team of the Novartis Cell and Gene Therapy Unit as the Global Program Head of Stem Cell Transplant and early programs from 2014 through 2016. Dr. Sanna served as Global Head of Strategic Planning and Portfolio Management at the Novartis Institutes for BioMedical Research from 2010 through 2014. Dr. Sanna has served as a member of the Board of Directors of Adicet Bio, Inc., a biotechnology company since December 2020. Dr. Sanna received a Ph.D. in Biotechnology from the University of Sassari.

Dr. Tatsis is our Executive Vice President, Chief Regulatory and Quality Officer, a position she has held since August 2020. Previously, she was our Senior Vice President and Chief Regulatory Officer from October 2019 to August 2020, and our Senior Vice President, Global Regulatory Affairs from September 2017 to October 2019. Prior to joining Vertex, Dr. Tatsis held positions of increasing responsibility at several pharmaceutical companies, including Sanofi, Stemnion, Pfizer, and Wyeth. Most recently, from 2014 to 2017, she was Vice President, Head of Global Regulatory Affairs, at the Sanofi Genzyme Business Unit focused on Inflammation/Immunology, Rare Disease, Multiple Sclerosis, Ophthalmology, Neurology, and Oncology/Immuno-Oncology. Dr. Tatsis also worked as an associate staff scientist and research fellow in Immunology and Vaccine Development at the Wistar Institute and completed a post-doctoral research fellowship in Immunology at Thomas Jefferson University. She received her Ph.D. in Cell and Molecular Biology from the University of Vermont and holds a B.S. in Biology from Temple University.

Mr. Wagner is our Executive Vice President and Chief Financial Officer, a position he has held since April 2019. Prior to joining Vertex, Mr. Wagner was Chief Financial Officer and Executive Vice President, Finance, of Ortho Clinical Diagnostics, a Carlyle Group portfolio company, from June 2015 to March 2019. In that role, he led the finance, accounting, tax, treasury, global financial systems, lender relations, and acquisitions and divestiture groups, and also had shared leadership for several enterprise-wide projects. From July 2012 to June 2015, Mr. Wagner served as Executive Vice President, Chief Financial Officer of Bruker Corporation, a scientific instruments manufacturer. Prior to that, Mr. Wagner served as Chief Financial Officer for Progress Software Corporation, a provider of enterprise software, and Millipore Corporation, a global provider of products and services in the life science tools market. Mr. Wagner served as a director and chairman of the Audit Committee of Good Start Genetics, Inc., a molecular diagnostics company, from April 2014 to August 2017 and served as a director and member of the Audit Committee of Bruker Corporation from August 2010 to June 2012. Mr. Wagner holds a B.S. in Accounting from Boston College and a M.B.A from Harvard Business School.

Ms. Ambrose is our Senior Vice President, Chief Accounting Officer, a position she has held since May 2021. Ms. Ambrose previously served as our Senior Vice President, Accounting, Tax, Treasury, Strategic Sourcing and Corporate Services since March 2021. From February 2003 until she joined Vertex, Ms. Ambrose held roles of increasing responsibility at Boston Scientific Corporation, a medical device company, most recently as Vice President of Finance and Controller of the Global Endoscopy Division from July 2019 to March 2021 and as Vice President of Global Internal Audit from February 2017 to June 2019. Prior to Boston Scientific Corporation, Ms. Ambrose served as an accountant at Ernst & Young LLP. She received her B.S. in Commerce from the University of Virginia and is a Certified Public Accountant.

ITEM 1A. RISK FACTORS

Investing in our common stock involves a high degree of risk, and you should carefully consider the risks and uncertainties described below in addition to the other information included or incorporated by reference in this Annual Report on Form 10-K. If any of the following risks or uncertainties actually occurs, our business, financial condition or results of operations would likely suffer, possibly materially. In that case, the trading price of our common stock could decline.

SUMMARY OF RISK FACTORS

Our business is subject to numerous risks and uncertainties, discussed in more detail in the following section. These risks include, among others, the following key risks:

Risks Related to Our Business

- We invest significant resources in the research and development of therapies for serious diseases other than CF, and if we are unable to successfully commercialize one or more of these therapies, our business could be materially harmed.
- All of our product revenues and the vast majority of our total revenues are derived from sales of medicines for the treatment of CF. If we are unable to continue to increase revenues from sales of our CF medicines, our business would be materially harmed and the market price of our common stock would likely decline.
- If our competitors bring products with superior product profiles to market, our products may not be competitive and our revenues could decline.
- If we discover safety issues with any of our products or if we fail to comply with continuing U.S. and applicable foreign regulations, commercialization efforts for the product could be negatively affected, the approved product could lose its approval or sales could be suspended, and our business could be materially harmed.
- If physicians and patients do not accept our products, or if patients do not remain on treatment or comply with their prescribed dosing regimen, our product revenues would be materially harmed in future periods.
- Government and other third-party payors seek to contain costs of health care through legislative and other means. If they fail to provide coverage and adequate reimbursement rates for our products, our revenues will be harmed.
- We may experience incremental pricing pressure on our products, which could reduce our revenues and future profitability.
- Current health care laws and regulations in the U.S. and future legislative or regulatory reforms to the U.S. health care system may affect our ability to commercialize our marketed products profitably.
- We have experienced challenges commercializing products outside of the U.S., and our future revenues will be dependent on our ability to obtain adequate reimbursement for our products.
- We have limited experience developing and commercializing cell and genetic therapies and could experience challenges with these programs, which could result in delays or prevent the development, manufacturing and commercialization of our cell and genetic therapies.

Risks Related to Development and Clinical Testing of Our Products and Product Candidates

- Our product candidates remain subject to clinical testing and regulatory approval, and our future success is dependent on our ability to successfully develop additional product candidates for both CF and non-CF indications.
- If we are unable to obtain or are delayed in obtaining regulatory approval, we may incur additional costs, experience delays in commercialization, or be unable to commercialize our product candidates.
- If clinical trials are prolonged or delayed, our development timelines for the affected development program could be extended, our costs to develop the product candidate could increase and the competitive position of the product candidate could be adversely affected.
- Difficulty in enrolling patients could delay or prevent clinical trials of our product candidates, and ultimately delay or prevent regulatory approval.

Risks Related to Government Regulation

- If regulatory authorities interpret any of our conduct, including our marketing practices, as being in violation of applicable health care laws, including fraud and abuse laws, laws prohibiting off-label promotion, disclosure laws or other similar laws, we may be subject to civil or criminal penalties.
- If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs in the U.S., we could be subject to additional reimbursement requirements, penalties, sanctions and fines that could have a material adverse effect on our business, financial condition, results of operations and growth prospects.
- If our processes and systems are not compliant with regulatory requirements, we could be subject to restrictions on marketing our products or could be delayed in submitting regulatory filings seeking approvals for our product candidates.
- We are subject to various and evolving laws and regulations governing the privacy and security of personal data, and our failure to comply could adversely affect our business, result in fines and/or criminal penalties, and damage our reputation.

Risks Related to Business Development Activities

- Our ability to execute on our long-term strategy depends in part on our ability to engage in transactions and collaborations with other entities that add to our pipeline or provide us with new commercial opportunities.
- We may not realize the anticipated benefits of acquisitions of businesses or technologies, and the integration following any such acquisition may disrupt our business and management.
- We face risks in connection with existing and future collaborations with respect to the development, manufacture and commercialization of our products and product candidates.
- We may not be able to attract collaborators or external funding for the development and commercialization of certain of our product candidates.

Risks Related to Supply, Manufacturing and Reliance on Third Parties

- We depend on third-party manufacturers and our internal capabilities to manufacture our products and the materials we require for our clinical trials. We may not be able to maintain our third-party relationships and could experience supply disruptions outside of our control.
- We rely on third parties to conduct pre-clinical work, clinical trials and other activities, and those third parties may not perform satisfactorily, including failing to meet established deadlines for the completion of such studies and/or trials or failing to satisfy regulatory requirements.

Risks Related to Intellectual Property

- If our patents do not protect our products or our products infringe third-party patents, we could be subject to litigation which could result in injunctions preventing us from selling our products or substantial liabilities.
- Uncertainty over intellectual property in the pharmaceutical and biotechnology industry has been the source of litigation and other disputes, that are inherently costly and unpredictable.
- We may be subject to claims by third parties asserting that our employees or we have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Risks Related to Our Operations

- Risks associated with operating in foreign countries could materially adversely affect our business.
- If we fail to attract and retain skilled employees, our business could be materially harmed.
- We are subject to risks associated with the COVID-19 pandemic.

Risks Related to Financial Results and Holding Our Common Stock

- Our stock price may fluctuate.
- Our effective tax rate fluctuates, and changes in tax laws, regulations and treaties, unfavorable resolution of tax contingencies or exposure to additional income tax liabilities could have a material impact on our future taxable income.

Risks Related to Our Business

We invest significant resources in the research and development of therapies for serious diseases other than CF, and if we are unable to successfully commercialize one or more of these therapies, our business could be materially harmed.

We invest significant resources in the research and development of medicines for serious diseases including SCD, beta thalassemia, APOL1-mediated kidney disease, T1D, pain, AATD, DMD and DM1. Some of these programs have progressed into clinical trials, while others are still in pre-clinical development. Product development is highly uncertain and expensive, and product candidates that may appear promising in the early phases of research and development may fail to reach commercial success for many reasons, including the failure to demonstrate acceptable clinical trial results or obtain marketing approval, the inability to manufacture or commercialize the product candidate on economically feasible terms, or the appearance of safety issues. For example, in June 2021, we decided not to progress VX-864, a drug candidate for the treatment of AATD, into late-stage development based on data obtained from a Phase 2 clinical trial.

Even if we gain marketing approval for one or more pipeline products, we cannot be sure that we will obtain market acceptance or adequate reimbursement levels from third-party payors or foreign governments for such products. Additionally, many of the therapies that we are developing in our pipeline target rare diseases that affect a limited number of patients. There can be no guarantee that we will effectively identify patients that are eligible for enrollment in our clinical trials or treatment with our product candidates. Even if we do successfully identify eligible patients, the number of patients that our product candidates are able to treat may turn out to be lower than we expect or new patients may become increasingly difficult to identify, each of which may adversely affect our revenues and materially harm our business. For these and other reasons, we may never be successful in expanding our pipeline and future revenue may continue to depend on sales of our CF medicines.

All of our product revenues and the vast majority of our total revenues are derived from sales of medicines for the treatment of CF. If we are unable to continue to increase revenues from sales of our CF medicines, our business would be materially harmed and the market price of our common stock would likely decline.

Our net product revenues and the vast majority of our total revenues are derived from the sale of our CF medicines. As a result, our future success is largely dependent upon our ability to increase revenues from sales of our CF medicines. This will require us to continue to gain approval and reimbursement for our triple combination therapy in ex-U.S. markets and successfully develop and commercialize our triple combination therapy for younger children with CF.

Our concentrated source of revenues presents a number of risks to our business, including:

- that one or more competing therapies may be developed successfully as a treatment for people with CF;
- that reimbursement policies of payors and other third parties may make it difficult to obtain reimbursement or reduce the net price we receive for our products;
- that we may experience manufacturing or supply disruptions for our CF medicines; and
- that we may experience adverse developments with respect to development or commercialization of our CF medicines and/or CF product candidates.

If any of the above risks were to materialize, if we are otherwise unable to increase revenues from sales of our CF medicines, or if we do not meet the expectations of investors or public equity market analysts, our business would be materially harmed and our ability to fund our operations could be adversely affected. For example, if we are unable to increase revenues from sales of our CF medicines, our ability to fund our research and development programs for the discovery and development or acquisition of new products would be harmed, which would limit our ability to diversify our revenue base and our stock price would likely be adversely affected.

If our competitors bring products with superior product profiles to market, our products may not be competitive and our revenues could decline.

A number of companies are seeking to identify and develop product candidates for the treatment of CF and other therapeutic areas we are targeting with our research and development activities. Our success in rapidly developing and commercializing our CF medicines may increase the resources that our competitors allocate to the development of potential

competitive treatments. If one or more competing therapies are successfully developed as a treatment for people with CF or any of the other diseases we are currently targeting in our pipeline, our products and our net product revenues could face competitive pressures. If one or more competing therapies prove to be superior to our then existing products and/or product candidates, our business could be materially adversely affected.

In addition, our business faces competition from major pharmaceutical companies possessing substantially greater financial resources than we possess. We also face competition from numerous smaller public and private companies, academic institutions, government agencies, public and private research organizations, and charitable venture philanthropy organizations that conduct research, seek patent protection, and/or establish collaborative arrangements for research, development, manufacturing, and commercialization.

Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early-stage companies also may prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Our products and any products that we develop in the future may not be able to compete effectively with marketed drugs or new drugs that may be developed by competitors. The risk of competition is particularly important to our company because substantially all of our revenues are related to the treatment of people with CF. There are many other companies developing products for the same patient populations that we are pursuing. In order to compete successfully in these areas, we must demonstrate improved safety, efficacy and/or tolerability, ease of manufacturing, and gain and maintain market acceptance over competing products.

If we discover safety issues with any of our products or if we fail to comply with continuing U.S. and applicable foreign regulations, commercialization efforts for the product could be negatively affected, the approved product could lose its approval or sales could be suspended, and our business could be materially harmed.

Our products are subject to continuing regulatory oversight, including the review of additional safety information. Products are more widely used by patients once approval has been obtained and therefore side effects and other problems may be observed after approval that were not seen or anticipated, or were not as prevalent or severe, during pre-approval clinical trials or nonclinical studies. The subsequent discovery of previously unknown or underestimated problems with a product could negatively affect commercial sales of the product, result in restrictions on the product or lead to the withdrawal of the product from the market. Each of our CF products shares at least one active pharmaceutical ingredient with another of our products. As a result, if any of our CF products were to experience safety issues, our other CF products may be adversely affected. The reporting of adverse safety events involving our products or public speculation about such events could cause our stock price to decline or experience periods of volatility. Our business also may be materially harmed by impaired sales of our products, denial or withdrawal of regulatory approvals, required label changes or additional clinical trials, reputational harm, or government investigations or lawsuits brought against us.

In addition, our products are subject to ongoing regulatory requirements governing the testing, manufacturing, labeling, packaging, storage, advertising, promotion, sale, distribution, import, export, recordkeeping, and submission of safety and other post-market information. We and our third-party manufacturers must comply with cGMP and other applicable regulations governing the manufacturing and distribution of our products. Regulatory authorities periodically inspect our drug manufacturing facilities, and those of our third-party manufacturers, to evaluate compliance with cGMP and other regulatory requirements.

If we or our collaborators, or third-parties acting on our behalf, fail to comply with applicable continuing regulatory requirements, we or our collaborators may be subject to fines, suspension or withdrawal of regulatory approvals for specific products, product recalls and seizures, operating restrictions and/or criminal prosecutions, any of which could have a material adverse effect on our business, reputation, financial condition, and results of operations.

If physicians and patients do not accept our products, or if patients do not remain on treatment or comply with their prescribed dosing regimen, our product revenues would be materially harmed in future periods.

Our medicines may not gain or maintain market acceptance among physicians and patients or other members of the

medical community. Effectively marketing our products and any of our product candidates or investigational therapies, if approved, requires substantial efforts, both prior to launch and after approval. Physicians may elect not to prescribe our products or recommend our cell or genetic therapies, and patients may elect not to take them or receive them or they may discontinue use of our products after initiation of treatment, for a variety of reasons including:

- prevalence and severity of adverse side effects;
- lack of reimbursement availability from third-party payors, including governmental entities;
- lower demonstrated efficacy, safety and/or tolerability compared to alternative treatment methods;
- lack of cost-effectiveness;
- a decision to wait for the approval of other therapies in development that have significant perceived advantages over our product;
- convenience and ease of administration;
- limitations or warnings contained in the labeling;
- the timing of market introduction of our product as well as competitive products;
- other potential advantages of alternative treatment methods; and
- inadequate sales, marketing and/or distribution support, including as a result of limitations or restrictions resulting from COVID-19.

If our medicines fail to achieve or maintain market acceptance, we may not be able to generate significant revenues in future periods.

Government and other third-party payors seek to contain costs of health care through legislative and other means. If they fail to provide coverage and adequate reimbursement rates for our products, our revenues will be harmed.

Sales of our products depend in part upon the availability of reimbursement from third-party payors. Third-party payors include government health programs such as Medicare and Medicaid in the U.S. and the national health care systems in ex-U.S. markets, managed care providers, private health insurers and other organizations. The trend in the health care industry is cost containment, and efforts of third-party payors to contain or reduce health care costs may adversely affect our ability to establish or maintain appropriate prices for our products or any drugs that we may develop and commercialize.

In most ex-U.S. markets, the pricing and reimbursement of therapeutic and other pharmaceutical products is subject to governmental control, and government authorities are making greater efforts to limit or regulate the price of drug products. In the U.S., there have been, and we expect that there will continue to be, a number of federal and state proposals to implement governmental controls that are similar to those that currently exist in Europe. For example, the ACA required manufacturers of Medicare Part D brand name drugs to provide discounts on those drugs to Medicare Part D beneficiaries during the coverage gap; increased the rebates paid by pharmaceutical companies to state Medicaid programs on drugs covered by Medicaid; and imposed an annual fee, which increases annually, on sales by branded pharmaceutical manufacturers.

Third-party payors throughout the world also have been attempting to control drug spending in light of the global economic pressures, including due to the global COVID-19 pandemic. In reimbursement negotiations, many payors are requesting price discounts and caps on total expenditures and limiting both the types and variety of drugs that they will cover if they are not able to secure them. As part of these negotiations, many ex-U.S. government payers also are requiring companies to establish product cost-effectiveness as a condition of reimbursement. These cost-effectiveness reviews may not account for many of the benefits provided by innovative medicines, and for the most part, have not taken into account the specific circumstances of products that treat rare diseases. This has led to conclusions that certain medicines, including our products in certain jurisdictions, are not cost-effective. As a result, certain countries have declined to reimburse, or delayed their reimbursement of, some of our products. Although not mandated in the U.S., various organizations have started advocating for cost-effectiveness analyses in the U.S. as well as value-based contracting in which the amount of reimbursement for a product is based on patient outcomes and other clinical or economic metrics related to the performance of such product. If U.S. payors were to adopt such assessments and make negative coverage determinations or utilize value-

based contracts that result in penalties to, or lower rates of, reimbursement, it could adversely affect our product revenues. Our business would be materially adversely affected if we are not able to obtain or maintain coverage and reimbursement of our products from third-party payors on a broad, timely, or satisfactory basis, or if such coverage is subject to overly broad or restrictive utilization management controls.

The increasing availability and use of innovative specialty pharmaceuticals for rare diseases, combined with their relative higher cost as compared to other types of pharmaceutical products, is generating significant third-party payor interest in developing cost-containment strategies targeted to this sector. Government regulations in both U.S. and ex-U.S. markets could further limit the prices that can be charged for our products and may limit our commercial opportunity. The increasing use of cost-effectiveness assessments in markets around the world and the financial challenges faced by many governments may lead to significant adverse effects on our business.

We may experience incremental pricing pressure on our products, which could reduce our revenues and future profitability.

There also has been an increase in state legislation and regulations related to drug pricing and drug pricing transparency. In the U.S., various states, including Nevada, Maryland, Louisiana, New York, California, Washington, Massachusetts, Connecticut, Vermont, New Hampshire, Utah, Minnesota, Oregon, Colorado, New Mexico, Virginia, Maine, Texas, North Dakota, and West Virginia, have passed legislation requiring companies to disclose extensive information relating to drug prices, drug price increases, and spending on research, development, and marketing, among other things. Although it is not always clear what states will do with the collected information, some laws were designed to obtain additional product discounts. We may continue to see more state action requiring additional disclosures or other actions. In addition, we could see increased federal activity related to drug pricing and transparency requiring disclosures or other actions instead of, or in addition to, state requirements. Similar initiatives also are occurring in, or being considered by, some of our ex-U.S. markets, including Italy and Brazil.

Complying with these laws can be expensive and requires significant personnel and operational resources. Additionally, any additional required discounts would adversely affect the pricing of, and revenues from, our products. Finally, while we seek to comply with all statutory and regulatory requirements, we face increased enforcement activity by the U.S. federal government, state governments, and private payors against pharmaceutical and biotechnology companies for pricing and reimbursement-related issues as well as inquiries from the U.S. Congress.

Other federal activities seeking to specifically address drug pricing and reimbursement include:

- rulemaking related to importation of prescription drugs from Canada, as well as guidance related to importation of prescription drugs from other foreign countries;
- attempts to establish reference pricing for certain physician-administered drugs;
- executive orders relating to drug pricing that are intended to broadly impact the pharmaceutical industry;
- changes to the federal anti-kickback statute safe harbors that eliminate anti-kickback statute discount safe harbor protection for certain manufacturer rebate arrangements;
- support for legislation allowing direct negotiation in Medicare Part D; and
- legislation relating to drug pricing, including bills that would impose rebate obligations for Medicare (and potentially other utilization) for price increases greater than the rate of inflation, require drug pricing negotiations in Medicare, redesign the Part D benefit to lower patient costs and overall spending, and introduce enhanced transparency measures into drug pricing.

We expect government scrutiny over drug pricing, reimbursement, and distribution to continue. Potential future government regulation of drug prices or reimbursement creates uncertainties about our portfolio and could have a material adverse effect on our operations.

Current health care laws and regulations in the U.S. and future legislative or regulatory reforms to the U.S. health care system may affect our ability to commercialize our marketed products profitably.

The U.S. government, individual states and some foreign jurisdictions also have been aggressively pursuing legislative

and regulatory reforms that could affect our ability to sell products. For example, in the U.S., there have been federal legislative and administrative efforts to repeal, substantially modify, or invalidate some or all of the provisions of the ACA, which could affect coverage and payment for medicines. The federal government additionally has proposed and enacted legislation leading to aggregate reductions of Medicare payments to providers, which ultimately could affect utilization of medicines.

Other reforms include the Bipartisan Budget Act of 2018, which contained various provisions that affect coverage and reimbursement of drugs, including an increase in the discount that manufacturers of Medicare Part D brand name drugs must provide to Medicare Part D beneficiaries during the coverage gap from 50% to 70%. These new laws or any other similar laws introduced in the future may result in additional reductions in Medicare and other health care funding, which could negatively affect our customers and accordingly, our financial operations. Moreover, payment methodologies may be subject to changes in health care legislation and regulatory initiatives. For example, CMS may develop new payment and delivery models, such as bundled payment models.

There also are a number of ongoing activities, including the Build Back Better Act, that could affect drug pricing in the Medicare and Medicaid programs. Those activities seek to reduce or limit the prices of drugs, make them more affordable for patients, reform Medicare Part D pharmaceutical benefits, bring more transparency to drug prices, require data collection and reporting of information such as rebates, fees, and other remuneration provided by drug manufacturers, and enable the government to negotiate prices.

Adoption of new health care reform legislation at the federal or state level could affect demand for, or pricing of, our products or product candidates if approved for sale. We cannot, however, predict the ultimate content, timing, or effect of any health care reform legislation or action, or its impact on us, including increased compliance requirements and costs, all of which may adversely affect our future business, operations, and financial results.

We have experienced challenges commercializing products outside of the U.S., and our future revenues will be dependent on our ability to obtain adequate reimbursement for our products.

In most ex-U.S. markets, the pricing and reimbursement of therapeutic and other pharmaceutical products is subject to governmental control. Given recent global economic pressures, including due to the COVID-19 pandemic, and geopolitical uncertainty, government authorities throughout the world are increasingly attempting to limit or regulate the price of drug products. The reimbursement process in ex-U.S. markets can take a significant time to conclude and reimbursement decisions are made on a country-by-country or region-by-region basis.

Our medicines treat life-threatening conditions and address relatively small patient populations, and our research and development programs are primarily focused on developing medicines to treat similar diseases. Particular attention is being paid by payors, including government and private payors, to these types of high-cost medicines, and countries are increasingly refusing to reimburse costly medicines. We have experienced challenges in obtaining timely reimbursement for our products in various countries outside the U.S. For example, we obtained reimbursement for ORKAMBI and SYMKEVI in England in the fourth quarter of 2019, four years after ORKAMBI's initial approval in 2015. Our future product revenues, including from TRIKAFTA/KAFTRIO, depend on, among other things, our ability to complete reimbursement discussions in ex-U.S. markets for our products. There is no assurance that coverage and reimbursement will be available outside of the U.S. for our four approved medicines or any future medicine, and, even if it is available, whether the timing or the level of reimbursement will be sufficient to allow us to market our medicines. Adverse pricing limitations or a delay in obtaining coverage and reimbursement would decrease our future net product revenues and harm our business.

We have limited experience developing and commercializing cell and genetic therapies and could experience challenges with these programs, which could result in delays or prevent the development, manufacturing and commercialization of our cell and genetic therapies.

We are investing significant resources in the research, development, manufacturing, and commercialization of cell and genetic therapies. While we have previously successfully developed, manufactured, and commercialized several small molecule drugs, we have limited experience with the development, manufacture, and commercialization of cell and genetic therapies. Development, manufacturing, and commercialization of cell and genetic therapies are subject to the same risks and uncertainties as small molecules. In addition:

- the manufacturing processes for cell and genetic therapies are different and more complex than the manufacturing processes required for small molecule drugs and require different systems, equipment, facilities, and expertise to develop and maintain;
- we may encounter difficulties in the production of our cell and genetic therapies and ensuring that the product meets required specifications;
- there have been a limited number of regulatory approvals for genetic therapies to date, the regulatory requirements governing genetic therapies continue to evolve, and regulatory positions and interpretations can change or lead to delays or significant unexpected costs with respect to our genetic therapy programs;
- the commercial success of cell or genetic therapies, including CTX001 and VX-880, if approved, will depend in part on the medical community, patients, governments, and third-party or governmental payers accepting cell or genetic therapy products in general, and the applicable medicine as medically useful, cost-effective, ethical, and safe; and
- market acceptance will be dependent in part on the prevalence and severity of side effects associated with the procedure by which the cell or genetic therapy is administered, including, with respect to CTX001 and VX-880, if approved, the prevalence and severity of any side effects resulting from the myeloablative preconditioning regime or immunosuppression, respectively.

For programs addressing rare genetic diseases with small patient populations, we may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics, to complete our clinical studies in an adequate and timely manner. Additionally, patients may be unwilling to participate in our clinical trials because of concerns that cell and genetic therapies are unsafe or unethical, negative publicity from adverse events in the biotechnology or gene therapy industries, or for other reasons, including competitive clinical studies for similar patient populations. Moreover, adverse developments in clinical trials conducted by others of cell and genetic therapy products or products created using similar technology, or adverse public perception of the field of cell and genetic therapies, may cause the FDA and other regulatory bodies to revise the requirements for approval of any cell or genetic therapy product candidates we may develop or limit the use of products utilizing technologies such as ours, either of which could materially harm our business.

As we advance our cell and genetic therapy product candidates, we will be required to consult with various regulatory authorities, and we must comply with applicable laws, rules, and regulations, which may change from time to time, including during the course of development of our cell and genetic therapy product candidates. If we fail to do so, we may be required to delay or discontinue the clinical development of certain of our cell and genetic therapy product candidates. These additional processes may result in a review and approval process that is longer than we otherwise would have expected. Even if we comply with applicable laws, rules, and regulations, and even if we maintain close coordination with the applicable regulatory authorities with oversight over our cell and genetic therapy product candidates, our development programs may fail to succeed. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential cell or genetic therapy product to market would materially adversely affect our business, financial condition, results of operations and prospects.

The regulatory approval process and clinical trial requirements for cell and genetic therapies can be more expensive and take longer than for other, better known or more extensively studied product candidates, and regulatory requirements governing cell and genetic therapy products have changed frequently and may continue to change in the future. For example, the FDA established the Office of Tissues and Advanced Therapies within its Center for Biologics Evaluation and Research, or CBER, to consolidate the review of cell therapies and related products, and the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its review. These and other regulatory review agencies, committees and advisory groups and the requirements and guidelines they promulgate, may lengthen the regulatory review process, require us to perform additional preclinical studies or clinical trials, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of these treatment candidates or lead to significant post-approval limitations or restrictions.

In order to develop and commercialize any future cell or genetic therapies, we will need to incur substantial expenditures to develop, contract for, or otherwise arrange for the necessary manufacturing capabilities. Additionally, the manufacture of cell and genetic therapies requires significant expertise. Even with the relevant experience and expertise, manufacturers of cell and genetic therapy products often encounter difficulties in production, including difficulties with production costs and yields, quality control, and compliance with federal, state and foreign regulations. We cannot make any assurances that these

problems will not occur, or that we will be able to resolve or address problems that occur in a timely manner, or at all.

To the extent we develop capabilities internally, there are many risks that could result in delays and additional costs, including the need to hire and train qualified employees and obtain access to necessary equipment and third-party technology. To the extent we partner with third parties to manufacture our cell or genetic therapies, the complexity in the manufacture of our products and product candidates may require lengthy technology transfers. In addition, the third parties on which we rely to manufacture our cell or genetic therapies may experience their own compliance challenges or delays.

We also face uncertainty as to whether cell and gene therapy treatments will gain the acceptance of the public or the medical community. If we obtain regulatory approval, the commercial success of cell and gene therapy treatments will depend, in part, on the acceptance of physicians, patients, and third-party payers of gene therapy products in general, and our product candidates in particular, as medically necessary, cost-effective, and safe. In particular, our success will depend upon physicians prescribing our product candidates in lieu of existing treatments they are already familiar with and for which greater clinical data may be available. Moreover, physicians and patients may delay acceptance of cell and gene therapy product candidates until the product candidates have been on the market for a certain amount of time. In addition, medical centers that administer procedures accompanying treatment could experience capacity constraints, and these centers are subject to competing priorities that could delay patient access to procedures associated with cell and gene therapy products. Negative public opinion or more restrictive government regulations may delay or impair the successful commercialization of, and demand for, cell and gene therapies.

There also is significant uncertainty related to the insurance coverage and reimbursement of cell or genetic therapy products, including gene therapies that are potential one-time treatments. It is difficult to predict what third party payors, including U.S. or ex-U.S. governments or private insurance companies, will decide with respect to reimbursement for novel cell and genetic therapies like the ones in our pipeline. Additionally, reimbursement rates for cell and genetic therapies approved before ours could create an adverse environment for reimbursement of any therapies we ultimately commercialize. The administration of our products may require procedures for the collection of cells from patients, followed by other procedures either before or after delivery of the cell or genetic therapy. The manner and level at which reimbursement is provided for these services also is important. An inadequate reimbursement for such services may adversely affect physician decision to recommend any product for which we obtain approval in the future and our ability to market or sell them.

Given there are only a few approved cell and genetic therapy products, it also is difficult to determine how long it will take or reasonably estimate the costs to develop, manufacture, and commercialize cell or genetic therapies. In addition, our cell-based therapies include approaches involving devices, which are subject to additional regulatory requirements. If we are unable to successfully develop, manufacture, or commercialize such therapies on a timely or profitable basis, or at all, we may not realize benefits or generate cash flows based on our investments in these programs and our business, financial condition, results of operations and our stock price would likely be adversely affected.

We are dependent upon a small number of customers for a significant portion of our revenue, and the loss of, or significant reduction in sales to, these customers would adversely affect our results of operations.

In the U.S., we sell our CF products principally to a limited number of specialty pharmacy and specialty distributors, which subsequently resell our products to patients and health care providers. Internationally, we sell our products primarily to a limited number of specialty distributors and retail chains, as well as hospitals and clinics. We expect this significant customer concentration in CF to continue for the foreseeable future. Our ability to generate and grow sales of our CF medicines will depend significantly on the extent to which these specialty distributors and specialty pharmacies are able to provide adequate distribution of our products to patients and healthcare providers. The loss of any large customer, a significant reduction in sales we make to them, any cancellation of orders they have made with us, or any failure to pay for the products we have shipped to them could adversely affect our business, financial condition, and results of operations.

Risks Related to Development and Clinical Testing of Our Products and Product Candidates

Our product candidates remain subject to clinical testing and regulatory approval, and our future success is dependent on our ability to successfully develop additional product candidates for both CF and non-CF indications.

Our business depends upon the successful development and commercialization of product candidates. These product candidates are in various stages of development and must satisfy rigorous standards of safety and efficacy before they can be approved for sale by the FDA or comparable foreign regulatory authorities. To satisfy these standards, we must allocate

resources among our various development programs and must engage in expensive and lengthy testing of our product candidates. Discovery and development efforts for new pharmaceutical and biological products, including new combination therapies, are resource-intensive and may take 10 to 15 years or longer for each product candidate. It is impossible to predict when or if any of our product candidates will prove effective and safe in humans or will receive regulatory approval. Despite our efforts, our product candidates may not:

- offer therapeutic or other improvement over existing competitive therapies;
- show the level of safety and efficacy, including the level of statistical significance, required by the FDA or other regulatory authorities for approval of a drug or biologic;
- meet applicable regulatory standards;
- be capable of being produced in commercial quantities at acceptable costs; or
- if approved for commercial sale, be successfully marketed as pharmaceutical or biological products.

We have recently completed and/or have ongoing or planned clinical trials for several of our product candidates. The strength of our product portfolio and pipeline will depend in large part upon the outcomes of these clinical trials, including clinical trials evaluating our triple combination therapy in younger children with CF, our next generation CF medicines, our Phase 3 clinical trials of CTX001, and our clinical trials of potential medicines to treat other diseases. Failure to advance product candidates through clinical development could impair our ability to ultimately commercialize products, which could materially harm our business and long-term prospects.

Results of our clinical trials and findings from our nonclinical studies, including toxicology findings in nonclinical studies conducted concurrently with clinical trials, could lead to abrupt changes in our development activities, including the possible cessation of development activities associated with a particular product candidate or program. For example, in June 2021, we announced that we had achieved our primary endpoint and established proof of mechanism in a Phase 2 clinical trial evaluating our Z-AAT corrector, VX-864. However, because the magnitude of treatment effect was unlikely to translate into substantial clinical benefit, we decided not to advance VX-864 into late-stage development.

Moreover, clinical data are often susceptible to varying interpretations, and many companies that have believed their product candidates performed satisfactorily in clinical trials have nonetheless failed to obtain marketing approval of their product candidate. Furthermore, results from our clinical trials may not meet the level of statistical significance or otherwise provide the level of evidence or safety and efficacy required by the FDA or other regulatory authorities for approval of a product candidate. Finally, clinical trials are expensive and require significant operational resources to implement and maintain.

Many companies in the pharmaceutical and biotechnology industries, including our company, have suffered significant setbacks in later-stage clinical trials even after achieving promising results in earlier-stage clinical trials. For example, the results from completed preclinical studies and clinical trials may not be replicated in later clinical trials, and ongoing clinical trials for our product candidates may not be predictive of the results we may obtain in later-stage clinical trials or of the likelihood of approval of a product candidate for commercial sale.

In addition, from time to time, we report interim, topline, and preliminary data from our clinical trials, which is based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change. Interim or preliminary data from a clinical trial may not be predictive of final results from the clinical trial and are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment and treatment continues and more patient data become available or as patients from our clinical trials continue other treatments for their disease. Topline data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, topline data should be viewed with caution until the final data are available. If the interim, topline, or preliminary data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, our product candidates may be harmed, which could harm our business, operating results, prospects or financial condition.

The ability of third parties to review and/or analyze data from our clinical trials, including as a result of government disclosure, also may increase the risk of commercial confidentiality breaches and result in enhanced scrutiny of our clinical trial results. For example, Clinical Trial Regulation (EU) No. 536/2014, or the Clinical Trial Regulation, and the EMA policy

on publication of clinical data for medicinal products for human use both permit the EMA to publish clinical information submitted in MAAs. Third party review and scrutiny could result in public misconceptions regarding our drugs and product candidates. These publications could also result in the disclosure of information to our competitors that we might otherwise deem confidential, which could harm our business.

If we are unable to obtain or are delayed in obtaining regulatory approval, we may incur additional costs, experience delays in commercialization, or be unable to commercialize our product candidates.

The time required to complete clinical trials and to satisfy the FDA and other countries' regulatory review processes is uncertain and typically takes many years. Our analysis of data obtained from nonclinical and clinical activities is subject to confirmation and interpretation by regulatory authorities, which could delay, limit or prevent regulatory approval. We also may encounter unanticipated delays or increased costs due to government regulation from future legislation or administrative action or changes in governmental policy during the period of drug development, clinical trials and governmental regulatory review.

We may seek a Fast Track, Priority Review, Breakthrough Therapy, and/or RMAT designation for some of our product candidates. Product candidates that receive one or more of these designations may be eligible for, among other things, a priority regulatory review. Each of these designations is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for Fast Track, Priority Review, Breakthrough Therapy and/or RMAT designation, the FDA may disagree and instead determine not to make such designation. The receipt of one or more of these designations for a product candidate does not guarantee a faster development process, review or approval compared to products developed or considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our products or product candidates qualifies for Fast Track, Priority Review, Breakthrough Therapy and/or RMAT designation, the FDA may later decide to withdraw such designation if it determines that the product or product candidate no longer meets the conditions for qualification.

Any failure to obtain regulatory approvals for a product candidate would prevent us from commercializing that product candidate. Any delay in obtaining required regulatory approvals could materially adversely affect our ability to successfully commercialize a product candidate. Furthermore, any regulatory approval to market a product may be subject to limitations that we do not expect on the indicated uses for which we may market the product. Any such limitations could reduce the size or demand of the market for the drug.

We also are subject to numerous foreign regulatory requirements governing the conduct of clinical trials, manufacturing and marketing authorization, pricing and third-party reimbursement. Non-U.S. jurisdictions have different approval procedures than those required by the FDA, and these jurisdictions may impose additional testing requirements for our product candidates. The foreign regulatory approval process includes all of the risks associated with the FDA approval process described above, as well as risks attributable to the satisfaction of foreign requirements. Approval by the FDA does not ensure approval by regulatory authorities outside the U.S. and approval by a foreign regulatory authority does not ensure approval by the FDA. In addition, although the FDA may accept data from clinical trials conducted outside the U.S., acceptance of this data is subject to conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with ethical principles. The trial population also must adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. In addition, while these clinical trials are subject to applicable local laws, FDA acceptance of the data will depend on its determination that the trials also complied with all applicable U.S. laws and regulations. If the FDA does not accept the data from any trial that we conduct outside the U.S., it would likely result in the need for additional trials, which would be costly and time-consuming and delay or permanently halt our development of the applicable product candidate.

If clinical trials are prolonged or delayed, our development timelines for the affected development program could be extended, our costs to develop the product candidate could increase and the competitive position of the product candidate could be adversely affected.

We cannot predict whether or not we will encounter problems with any of our completed, ongoing or planned clinical trials that will cause us or regulatory authorities to delay or suspend clinical trials, or delay the analysis of data from our completed or ongoing clinical trials. Among the factors that could delay our development programs are:

- ongoing discussions with the FDA or comparable foreign authorities regarding the scope or design of our clinical trials and the number of clinical trials we must conduct;
- failure or delay in reaching agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites;
- failure to add or delay in adding a sufficient number of clinical trial sites and obtaining IRB or independent ethics committee approval at each clinical trial site;
- suspension or termination of clinical trials of product candidates for various reasons, including non-compliance with regulatory requirements;
- clinical trial sites deviating from clinical trial protocol or dropping out of a clinical trial;
- delays in enrolling volunteers or patients into clinical trials, including as a result of low numbers of patients that meet the eligibility criteria for the trial;
- a lower than anticipated retention rate of volunteers or patients in clinical trials;
- the need to repeat clinical trials as a result of unfavorable or inconclusive results, unforeseen complications in testing or clinical investigator error;
- inadequate supply or deficient quality of product candidate materials or other materials necessary for the conduct of our clinical trials;
- unfavorable FDA or foreign regulatory authority inspection and review of a manufacturing facility that supplied clinical trial materials or its relevant manufacturing records or a clinical trial site or records of any clinical or preclinical investigation;
- unfavorable or inconclusive scientific results from clinical trials;
- serious and unexpected drug-related side-effects experienced by participants in our clinical trials or by participants in clinical trials being conducted by our competitors to evaluate product candidates with similar mechanisms of action or structures to therapies that we are developing;
- favorable results in testing of our competitors' product candidates, or FDA or foreign regulatory authority approval of our competitors' product candidates; or
- action by the FDA or a foreign regulatory authority to place a clinical hold or partial clinical hold on a trial or compound or deeming the clinical trial conduct as problematic.

For planning purposes, we estimate the timing of the accomplishment of various scientific, clinical, regulatory, and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of scientific studies and clinical trials and the submission of regulatory filings. From time to time, we publicly announce the expected timing of some of these milestones. All of these milestones are based on a variety of assumptions. The actual timing of these milestones can vary dramatically compared to our estimates, in many cases for reasons beyond our control. If we do not meet these milestones as publicly announced, the commercialization of our products may be delayed and the credibility of our estimates may be adversely affected and, as a result, our stock price may decline.

Difficulty in enrolling patients could delay or prevent clinical trials of our product candidates, and ultimately delay or prevent regulatory approval.

Our ability to enroll patients in our clinical trials in sufficient numbers and on a timely basis is subject to a number of factors. Clinical trials are expensive and require significant operational resources. Delays in patient enrollment or unforeseen drop-out rates may result in increased costs and longer development times. The enrollment of patients further depends on many factors, including:

- the proximity of patients to clinical trial sites;
- the size of the patient population, the nature of the protocol, and the design of the clinical trial;

- our ability to recruit clinical trial investigators with the appropriate competencies and experience;
- the number of other clinical trials ongoing and competing for patients in the same indication;
- our ability to obtain and maintain patient consents;
- reporting of the preliminary results of any of our clinical trials;
- the availability of effective treatments for the relevant disease and eligibility criteria for the clinical trial;
- the risk that patients enrolled in clinical trials will drop out of the clinical trials before clinical trial completion; and
- factors we may not be able to control, such as current or potential pandemics that may limit patients, principal investigators or staff or clinical site availability (e.g., the COVID-19 pandemic).

We, our collaborators, the FDA, or other applicable regulatory authorities may suspend clinical trials of a product candidate at any time if we or they believe the healthy volunteers or patients participating in such clinical trials are being exposed to unacceptable health risks or for other reasons. Any such suspension could materially adversely affect the development of a particular product candidate and our business.

Risks Related to Government Regulation

If regulatory authorities interpret any of our conduct, including our marketing practices, as being in violation of applicable health care laws, including fraud and abuse laws, laws prohibiting off-label promotion, disclosure laws or other similar laws, we may be subject to civil or criminal penalties.

We are subject to health care fraud and abuse laws, such as the FCA and the AKS, and other similar laws and regulations both in the U.S. and in non-U.S. markets.

In the U.S., the Federal Anti-Kickback Statute prohibits knowingly and willfully offering, paying, soliciting, receiving or providing remuneration, directly or indirectly, in exchange for or to induce either the referral of an individual, or the ordering, furnishing, arranging for or recommending of an item or service that is reimbursable, in whole or in part, by a federal health care program, such as Medicare or Medicaid. Because of the broad scope of the prohibition, most financial interactions between pharmaceutical manufacturers and prescribers, purchasers, third party payors and patients would be subject to the statute. Although there are a number of statutory exceptions and regulatory safe harbors protecting certain common activities from prosecution, the exceptions and safe harbors are narrow. Financial interactions must therefore be structured carefully to qualify for protection or otherwise withstand scrutiny.

Federal false claims laws, including the FCA, prohibit any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government, or knowingly making, or causing to be made, a false statement to get a false claim paid. Pharmaceutical companies have been prosecuted under these laws for a variety of alleged promotional and marketing activities, such as providing free product to customers with the expectation that the customers would bill federal programs for the product; reporting to pricing services inflated average wholesale prices that were then used by federal programs to set reimbursement rates; engaging in promotion for uses that the FDA has not approved, known as “off-label” uses, that caused claims to be submitted to Medicaid for those off-label uses; submitting inflated “best price” information to the Medicaid Rebate Program; and certain manufacturing-related violations. The scope of this and other laws may expand in ways that make compliance more difficult and expensive.

The FDA and other regulatory agencies closely regulate the post-approval marketing and promotion of products to ensure that they are marketed only for the approved indications and in accordance with the provisions of the approved labeling. Although physicians are permitted, based on their medical judgment, to prescribe products for indications other than those approved by the FDA, manufacturers are prohibited from promoting their products for such off-label uses. We market our products to eligible people with CF for whom the applicable product has been approved and provide promotional materials and training programs to physicians regarding the use of each product in these patient populations. These eligible people do not represent all people with CF. If the FDA determines that our promotional materials, training, or other activities constitute off-label promotion, it could request that we modify our training or promotional materials or other activities, conduct corrective advertising, or subject us to regulatory enforcement actions, including the issuance of a warning or untitled letter, injunction, seizure, civil fines and criminal penalties. It also is possible that other federal, state, or foreign

enforcement authorities might take action if they believe that the alleged improper promotion led to the submission and payment of claims for an off-label use, which could result in significant fines or penalties under other statutory authorities, such as laws prohibiting false claims for reimbursement. Even if it is later determined we were not in violation of these laws, we may be faced with negative publicity, incur significant expenses defending our actions, and have to divert significant management resources from other matters.

In the U.S., federal and state laws regulate financial interactions between pharmaceutical manufacturers and healthcare providers, require disclosure to government authorities and the public of such interactions, and mandate the adoption of compliance standards or programs. For example, the so-called federal "sunshine law" requires pharmaceutical manufacturers to report annually to CMS payments or other transfers of value made by that entity to physicians and teaching hospitals (and additional categories of health care practitioners beginning with reports submitted on or after January 1, 2022). We also have similar reporting obligations with respect to financial interactions throughout the E.U. We expended significant efforts to establish, and are continuing to devote significant resources to maintain and enhance, systems and processes in order to comply with these regulations. Requirements to track and disclose financial interactions with health care providers and organizations increase government and public scrutiny of these financial interactions. Failure to comply with the reporting requirements could result in significant civil monetary penalties.

The sales and marketing practices of our industry have been the subject of increased scrutiny from government authorities in the U.S. and other countries in which we market our products, and we believe that this trend will continue. Many of these laws have not been fully interpreted by the government authorities or the courts, and their provisions are subject to a variety of interpretations. While we have a corporate compliance program which, together with our policies and procedures, is designed to actively identify, prevent and mitigate risk through the implementation of compliance policies and systems and the promotion of a culture of compliance, if we are found not to be in full compliance with these laws and regulations, our business could be materially harmed. We may be subject to penalties, including civil and criminal penalties, damages, fines, exclusion from federal health care programs and/or the curtailment or restructuring of our operations. Even if we successfully defend against government challenge, responding to the challenge may cause us to incur significant legal expenses and divert our management's attention from the operation of our business.

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

We participate in the Medicaid Drug Rebate Program, the 340B Drug Pricing Program, and a number of other federal and state government pricing programs in the U.S. in order to obtain coverage for our products by certain government health care programs. These programs require us to pay rebates or provide discounts to certain government payers or private purchasers in connection with our products when dispensed to beneficiaries of these programs. In some cases, such as with the Medicaid Drug Rebate Program, the rebates are based on pricing and rebate calculations that we report on a monthly and quarterly basis to the government agencies that administer the programs. The terms, scope and complexity of these government pricing programs change frequently. For example, regulations finalized in December 2020 created an alternative Medicaid rebate formula for "line extensions" of oral solid dosage forms and revised regulations regarding manufacturer-sponsored patient benefit programs in the context of payor "accumulator" programs. Additionally, the expansion of the 340B Drug Discount Program through the ACA has increased the number of purchasers who are eligible for significant discounts on branded drugs. These and future changes to government pricing programs, laws, and regulations may have a material adverse impact on our revenue and operations.

We also may have reimbursement obligations or be subject to penalties if we fail to provide timely and accurate information to the government, pay the correct rebates, or offer the correct discounted pricing. Changes to the price reporting or rebate requirements of these programs would affect our obligations to pay rebates or offer discounts. For example, the removal of the current statutory 100% of Average Manufacturer Price per-unit cap on Medicaid rebate liability for single source and innovator multiple source drugs, effective as of January 1, 2024, under the American Rescue Plan Act of 2021 may affect the amount of rebates paid on prescription drugs under Medicaid and the prices that are required to be charged to covered entities under the 340B Drug Discount Program. Responding to current and future changes to these and other Medicaid Drug Rebate Program requirements may increase our costs and the complexity of compliance, will be time-consuming, and could have a material adverse effect on our results of operations.

If our processes and systems are not compliant with regulatory requirements, we could be subject to restrictions on marketing our products or could be delayed in submitting regulatory filings seeking approvals for our product candidates.

We have a number of regulated processes and systems that are required both prior to and following approval of our drugs and product candidates. These processes and systems are subject to continual review and periodic inspection by the FDA and other regulatory bodies. In addition, the clinical research organizations and other third parties that we work with in our non-clinical studies and clinical trials and our oversight of such parties are subject to similar reviews and periodic inspection by the FDA and other regulatory bodies. If compliance issues are identified at any point in the development and approval process, we may experience delays in filing for regulatory approval for our product candidates, or delays in obtaining regulatory approval after filing, if at all. Any later discovery of previously unknown problems or safety issues with approved drugs or manufacturing processes, or failure to comply with regulatory requirements, may result in restrictions on such drugs or manufacturing processes, withdrawal of drugs from the market, the imposition of civil or criminal penalties or a refusal by the FDA and/or other regulatory bodies to approve pending applications for marketing approval of new drugs or supplements to approved applications, any of which could have a material adverse effect on our business. In addition, we are party to agreements that transfer responsibility for complying with specified regulatory requirements, such as filing and maintenance of marketing authorizations and safety reporting or compliance with manufacturing requirements, to our collaborators and third-party manufacturers. If our collaborators or third-party manufacturers do not fulfill these regulatory obligations, any drugs for which we or they obtain approval may be subject to later restrictions on manufacturing or sale, which could have a material adverse effect on our business.

We are subject to various and evolving laws and regulations governing the privacy and security of personal data, and our failure to comply could adversely affect our business, result in fines and/or criminal penalties, and damage our reputation.

We are subject to data privacy and security laws and regulations in various jurisdictions that apply to the collection, storage, use, sharing, and security of personal data, including health information, and impose significant compliance obligations. In addition, numerous other federal and state laws, including state security breach notification laws, state health information privacy laws and federal and state consumer protection laws, govern the collection, use, disclosure and security of personal information. The legislative and regulatory landscape for privacy and data protection continues to evolve, and there has been an increasing focus on privacy and data protection issues with the potential to affect our business.

For example, the E.U. General Data Protection Regulation, or GDPR, went into effect in 2018 and has imposed new obligations on us with respect to our processing of personal data and the cross-border transfer of such data, including higher standards of obtaining consent, more robust transparency requirements, data breach notification requirements, requirements for contractual language with our data processors, and stronger individual data rights. Different E.U. member states have interpreted the GDPR differently and many have imposed additional requirements, which add to the complexity of processing personal data in the E.U. The GDPR also imposes strict rules on the transfer of personal data to countries outside the E.U., including the U.S. and the U.K., and permits data protection authorities to impose large penalties for violations of the GDPR. The GDPR rules related to cross border data transfers continue to evolve based on E.U. court decisions and regulator guidance, which presents certain practical challenges to compliance. Compliance with the GDPR is a rigorous and time-intensive process that may increase our cost of doing business or require us to change our business practices, and despite those efforts, there is a risk that we may be subject to fines and penalties, litigation, and reputational harm in connection with any activities falling within the scope of the GDPR.

In the U.S., California has passed the California Consumer Privacy Act (the “CCPA”), which went into effect on January 1, 2020. In November 2020, California also passed the California Privacy Rights Act (the “CPRA”), which expands and builds upon the consumer privacy rights of the CCPA. Certain other states have also enacted legislation governing the protection of personal data and several other states and the federal government are actively considering similar proposed legislation. Additionally, Brazil passed the General Data Protection Law, which went into effect in August 2020. While we continue to address the implications of the new data privacy regulations, data privacy remains an evolving landscape at both the domestic and international level, with new regulations coming into effect and continued legal challenges. Each law is also subject to various interpretations by courts and regulatory agencies, creating even more uncertainty. While we have a global privacy program that addresses such laws and regulations, our efforts to comply with the evolving data protection rules may be unsuccessful.

We must devote significant resources to understanding and complying with the changing landscape in this area. Failure to comply with data protection laws may expose us to risk of enforcement actions taken by data protection authorities, private

rights of action in some jurisdictions, and potential significant penalties if we are found to be non-compliant. Failure to comply with the GDPR and applicable national data protection laws of European Economic Area member states could lead to fines of up to €20,000,000 or up to 4% of the total worldwide annual revenue of the preceding financial year, whichever is higher. Some of these laws and regulations also carry the possibility of criminal sanctions. For example, while we are not directly subject to the Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, or HIPAA, we could be subject to penalties, including criminal penalties if we knowingly obtain or disclose individually identifiable health information from a HIPAA-covered health care provider or research institution that has not complied with HIPAA's requirements for disclosing such information. In addition, the commercialization of cell and gene therapies requires the collection and processing of a greater amount of personal data than traditional therapies, potentially increasing risk. Furthermore, the number of government investigations related to data security incidents and privacy violations continue to increase and government investigations typically require significant resources and generate negative publicity, which could harm our business and our reputation.

The COVID-19 pandemic has added further complexity to the processing of personal data. For example, safety measures and government health regulations intended to protect our employees, contractors, and other visitors to our sites may require the collection of certain personal data. Although we are focused on ensuring that personal data is properly protected, our efforts may be unsuccessful and we could unintentionally be subject to unauthorized access or disclosure of such personal data.

If we do not comply with laws regulating the protection of the environment and health and human safety, our business could be adversely affected.

Our research and development efforts involve the regulated use of hazardous materials, chemicals, and various controlled and radioactive compounds. Although we believe that our safety procedures for handling and disposing of these materials comply with the standards prescribed by state, federal and foreign regulations, the risk of loss of, or accidental contamination or injury from, these materials cannot be eliminated. If an accident occurs, we could be held liable for resulting damages, which could be substantial. We also are subject to numerous environmental, health, and workplace safety laws and regulations, including those governing laboratory procedures, exposure to blood-borne pathogens, and the handling of biohazardous materials. Although we maintain workers' compensation insurance to cover us for costs we may incur due to injuries to our employees resulting from the use of these materials, this insurance may not provide adequate coverage against potential liabilities. We maintain insurance to cover pollution conditions or other extraordinary or unanticipated events relating to our use and disposal of hazardous materials that we believe is appropriate based on the small amount of hazardous materials we generate. Additional federal, state and local laws and regulations affecting our operations may be adopted in the future. We may incur substantial costs to comply with, and substantial fines or penalties if we violate, any of these laws or regulations.

Risks Related to Business Development Activities

Our ability to execute on our long-term strategy depends in part on our ability to engage in transactions and collaborations with other entities that add to our pipeline or provide us with new commercial opportunities.

In order to achieve our long-term business objectives, we seek to license or acquire products, product candidates and other technologies that have the potential to complement our ongoing research and development efforts, access emerging technologies and license or acquire pipeline assets. These transactions may be similar to prior transactions, may be structured differently than prior transactions, or may involve larger transactions or later-stage assets. We have faced and will continue to face significant competition for the acquisition of rights to these types of products, product candidates and other technologies from a variety of other companies, many of which have significantly more financial resources and experience in business development activities than we have. In addition, non-profit organizations may be willing to provide capital to the companies that control additional products, product candidates or technologies, which may provide incentives for companies to advance these products, product candidates or technologies independently. Also, the cost of acquiring, in-licensing or otherwise obtaining rights to such products, product candidates or other technologies has grown dramatically in recent years and may be at levels that we cannot afford or that we believe are not justified by market potential. As a result, we may not be able to acquire, in-license or otherwise obtain rights to additional products, product candidates or other technologies on acceptable terms or at all.

We may not realize the anticipated benefits of acquisitions of businesses or technologies, and the integration following any such acquisition may disrupt our business and management.

It is challenging to effectively integrate businesses and technologies that we acquire, including the acquisitions of Semma and Exonics and the exclusive licenses that we have acquired from CRISPR and Moderna, and we may not realize the benefits anticipated from such transactions. Achieving the anticipated benefits of any transaction and successfully integrating acquired businesses or technologies involves a number of risks, including:

- failure to successfully develop and commercialize the acquired products, product candidates or technologies or to achieve other strategic objectives;
- delays or inability to progress preclinical programs into clinical development or unfavorable data from clinical trials evaluating the acquired or licensed product or product candidates;
- difficulty in integrating the products, product candidates, technologies, business operations and personnel of an acquired asset or company;
- disruption of our ongoing business and distraction of our management and employees from daily operations or other opportunities and challenges;
- the potential loss of key employees of an acquired company;
- entry into markets in which we have no or limited direct prior experience or where competitors in such markets have stronger market positions;
- potential failure of the due diligence processes to identify significant problems, liabilities or challenges of an acquired company, or acquired or licensed products, product candidate or technology, including but not limited to, problems, liabilities or challenges with respect to intellectual property, clinical or non-clinical data, safety, accounting practices, employee, or third-party relations and other known and unknown liabilities;
- liability for activities of the acquired company or licensor before the acquisition or license, including intellectual property infringement claims, violations of laws, commercial disputes, tax liabilities, and other known and unknown liabilities;
- exposure to litigation or other claims in connection with, or inheritance of claims or litigation risk as a result of an acquisition or license, including but not limited to, claims from terminated employees, customers, former equity holders or other third parties; and
- difficulties in the integration of the acquired company's departments, systems, including accounting, human resource and other administrative systems, technologies, books and records, and procedures, as well as in maintaining uniform standards, controls, including internal control over financial reporting required by the Sarbanes-Oxley Act of 2002 and related procedures and policies.

Acquisitions, licensing arrangements and other strategic transactions are inherently risky, and ultimately, if we do not complete an announced acquisition, collaboration or strategic transaction or integrate an acquired or licensed asset, business or technology successfully and in a timely manner, we may not realize the anticipated benefits of the strategic transaction.

We may later incur impairment charges related to assets acquired in any such transaction. Even if we achieve the long-term benefits associated with our strategic transactions, our expenses and short-term costs may increase materially and adversely affect our liquidity and short-term net income. Future strategic transactions could result in potentially dilutive issuances of equity securities, the incurrence of debt, the creation of contingent liabilities, impairment expenses related to goodwill, or impairment or amortization expenses related to other intangible assets, all of which could harm our financial condition.

We face risks in connection with existing and future collaborations with respect to the development, manufacture and commercialization of our products and product candidates.

The risks that we face in connection with our current collaborations, including CRISPR, and any future collaborations, include the following:

- Our collaborators may change the focus of their development and commercialization efforts or may have insufficient resources or expertise to effectively develop, manufacture or commercialize our product candidates.
- The ability of some of our therapies to reach their potential could be limited if collaborators are unable to effectively develop, manufacture or commercialize these therapies or product candidates or decrease or fail to increase development or commercialization efforts related to those therapies or product candidates. Our collaboration agreements allocate development, manufacturing and commercialization responsibilities between us and our collaborators and provide our collaborators with a level of discretion in determining the amount and timing of efforts and resources that they will apply to these collaborations.
- Our collaborators may have limited experience in developing, manufacturing and commercializing therapies, either generally, or in the specific therapeutic area.
- Collaboration agreements may have the effect of limiting the areas of research and development that we may pursue, either alone or in collaboration with third parties.
- Collaborators may develop and commercialize, either alone or with others, drugs that are similar to or competitive with the products or product candidates that are the subject of their collaborations with us.
- Disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or termination of the research, development or commercialization of product candidates, might lead to additional responsibilities or costs for us with respect to product candidates, or might result in litigation or arbitration. Any such disagreements would divert management attention and resources and would be time-consuming and expensive.
- Collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation.
- Collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability.
- Investigations and/or compliance or enforcement actions against a collaborator, which may expose us to indirect liability as a result of our partnership with such collaborator.
- Our collaboration agreements are subject to termination under various circumstances.
- We may be unable to control the resources our collaborators devote to our programs, products or product candidates, and the priorities and strategic objectives of our collaborators may not align precisely with ours.

Additionally, if a collaborator were to be involved in a business combination with a third party, it might de-emphasize or terminate the development or commercialization of any product candidate licensed to it by us. If one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and our perception in the business and financial communities could be harmed.

We may not be able to attract collaborators or external funding for the development and commercialization of certain of our product candidates.

As part of our ongoing strategy, we may seek additional collaborative arrangements or external funding for certain of our development programs and/or seek to expand existing collaborations to cover additional commercialization and/or development activities. We have a number of research programs and clinical development programs, some of which are being developed in collaboration with a third party. At any time, we may determine that in order to continue development of a product candidate or program or successfully commercialize a drug we need to identify a collaborator or amend or expand an

existing collaboration. For example, in April 2021, we amended and restated the original JDCA, positioning us to lead global development, manufacturing and commercialization of CTX001, with support from CRISPR.

Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA, EMA or other regulatory authorities, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of the applicable intellectual property, which can exist if there is a challenge to such ownership without regard to the merits of the challenge, and industry and market conditions generally. Potentially, and depending on the circumstances, we may desire that a collaborator either agree to fund portions of a drug development program led by us, or agree to provide all of the funding and directly lead the development and commercialization of a program. No assurance can be given that any efforts we make to seek additional collaborative arrangements will be successfully completed on a timely basis or at all. If we elect to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we are unable to enter into acceptable collaborative relationships, one or more of our development programs could be delayed or terminated and the possibility of our receiving a return on our investment in the program could be impaired.

Risks Related to Supply, Manufacturing and Reliance on Third Parties

We depend on third-party manufacturers and our internal capabilities to manufacture our products and the materials we require for our clinical trials. We may not be able to maintain our third-party relationships and could experience supply disruptions outside of our control.

We rely on a worldwide network of third-party manufacturers and our internal capabilities, including our own manufacturing facility in Boston, to manufacture product candidates for clinical trials as well as our medicines for commercial use. We could be subject to significant supply interruptions as a result of disruptions to third party or our internal manufacturing capabilities. Our supply chain for sourcing raw materials and manufacturing drug product ready for distribution, including obtaining necessary supplies, is a multi-step international endeavor. Third-party contract manufacturers, including some in China, perform different parts of our manufacturing process. Contract manufacturers may supply us with raw materials, convert these raw materials into drug substance and/or convert the drug substance into final dosage form. Third parties are used for packaging, warehousing and distribution of products. In cell and genetic therapies, third parties also will be used to both manufacture and deliver our therapies, which requires significant expertise and capacity to meet our requirements. This capacity may be limited by the number of other clinical trials and commercial manufacturing ongoing for other companies seeking similar support.

If third parties are unwilling or unable to meet our requirements, including as a result of the COVID-19 pandemic or because of their own supply or capacity issues, we could experience supply disruptions outside of our control. Additionally, manufacturing facilities, both foreign and domestic, are subject to inspections by the FDA and other U.S. and foreign government authorities. Although we actively engage with regulatory authorities, the timing of regulatory approvals for each of these facilities may be delayed for a variety of reasons, including as a result of the COVID-19 pandemic. In addition, we and the third parties with whom we engage are required to maintain compliance with quality regulations globally. An inability to maintain compliance with such regulations, including cGMP requirements, could cause significant disruptions to our business and operations.

Additionally, establishing, managing and expanding our global supply chain requires a significant financial commitment and the creation and maintenance of our numerous third-party contractual relationships. Although we attempt to manage the business relationships with companies in our supply chain, we could be subject to supply disruptions outside of our control.

Supply disruptions may result from a number of factors, including shortages in product raw materials, labor or technical difficulties, regulatory inspections or restrictions, shipping or customs delays, general global supply chain disruptions, or any other performance failure by us or any third-party manufacturer on which we rely. We may also experience supply disruptions if regulatory agencies are unable to inspect the manufacturing facilities on which we rely. Any such disruptions could disrupt sales of our products and/or the timing or advancement of our clinical trials.

While we have developed internal capabilities to supply product candidates for use in our clinical trials as well as our

medicines for commercial sale, a majority of the manufacturing steps needed to produce our medicines, product candidates, and drug products are performed through a third-party manufacturing network. We expect that we will continue to rely on third parties to meet our commercial supply needs and a significant portion of our clinical supply needs for the foreseeable future.

If we or our third-party manufacturers become unable or unwilling to continue manufacturing product and we are not able to promptly identify another manufacturer, we could experience a disruption in the commercial supply of our then-marketed medicines, which would have a significant effect on patients, our business, and our product revenues. Similarly, a disruption in the clinical supply of product candidates could delay the completion of clinical trials and affect timelines for regulatory filings. We have a limited number of critical steps in our manufacturing process that are single sourced, including for recently launched products. To ensure the stability of our supply chains, we continue to develop alternatives for our manufacturing processes. However, there can be no assurance that we will be able to establish and maintain additional manufacturers or capacity for all of our product candidates and products on a timely basis or at all.

In the course of providing its services, a contract manufacturer may develop process technology related to the manufacture of our products or product candidates that the manufacturer owns, either independently or jointly with us. This would increase our reliance on that manufacturer or require us to obtain a license from that manufacturer in order to have our products or product candidates manufactured by other suppliers utilizing the same process.

We rely on third parties to conduct pre-clinical work, clinical trials and other activities, and those third parties may not perform satisfactorily, including failing to meet established deadlines for the completion of such studies and/or trials or failing to satisfy regulatory requirements.

We rely on third parties such as CROs to help manage certain pre-clinical work and our clinical trials and on medical institutions, clinical investigators, and clinical research organizations such as the Therapeutic Development Network, which is primarily funded by the CFF, to assist in the design and review of, and to conduct our clinical trials, including enrolling qualified patients. In addition, we engage third party contractors to support numerous other research, commercial and administrative activities. Our reliance on these third parties for clinical development activities reduces our control over these activities but does not relieve us of our responsibilities. For example, we remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the clinical trial. Moreover, the FDA requires us to comply with standards, commonly referred to as good laboratory practices and good clinical practices, for conducting, recording and reporting the results of pre-clinical and clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Such standards, particularly with respect to newer cell and genetic therapies, will continue to evolve and subject us and third parties to new or changing requirements.

If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may be required to replace them. Although we believe that there are a number of other third-party contractors we could engage to continue the activities, it may result in a delay of the affected clinical trial, drug development program or applicable activity. If clinical trials are not conducted in accordance with our contractual expectations or regulatory requirements, action by regulatory authorities might significantly and adversely affect the conduct or progress of these clinical trials or in specific circumstances might result in a requirement that a clinical trial be redone. Accordingly, our efforts to obtain regulatory approvals for and commercialize our product candidates could be delayed. In addition, failure of any third-party contractor to conduct activities in accordance with our expectations, including as a result of the COVID-19 pandemic, could adversely affect the relevant research, development, commercial or administrative activity.

Risks Related to Intellectual Property

If our patents do not protect our products or our products infringe third-party patents, we could be subject to litigation which could result in injunctions preventing us from selling our products or substantial liabilities.

We own and/or control numerous issued patents and pending patent applications in the U.S., as well as counterparts in other countries. Our success will depend, in significant part, on our ability to obtain and defend U.S. and foreign patents covering our products, their uses and our processes, to preserve our trade secrets and to operate without infringing the proprietary rights of third parties. We cannot be certain that any patents will issue from our pending patent applications or, even if patents issue or have issued, that the issued claims will provide us with adequate protection against competitive products or otherwise be commercially valuable.

Due to evolving legal standards relating to the patentability, validity, and enforceability of patents covering pharmaceutical and biotechnological inventions and the scope of claims made under these patents, our ability to obtain, maintain and enforce patents is uncertain and involves complex legal and factual questions. Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents in the U.S. The Leahy-Smith America Invents Act, or the Leahy-Smith Act, made a number of significant changes to U.S. patent law in 2011. These include provisions that affect the way patent applications are prosecuted and may also affect patent litigation. For example, the first to file provisions limit the rights of an inventor who is the first to invent an invention but is not the first to file an application claiming that invention. U.S. and foreign patent applications typically are maintained in confidence for a period of time after they initially are filed with the applicable patent office. Consequently, we cannot be certain that we were the first to invent, or the first to file patent applications on, our products or product candidates or their use. If a third party also has filed a U.S. patent application relating to our products or product candidates, their uses, or a similar invention, we may have to participate in legal or administrative proceedings to determine priority of invention. For applications governed by the Leahy-Smith Act, if a third-party has an earlier filed U.S. patent application relating to our products or product candidates, their uses, or a similar invention, we may be unable to obtain an issued patent from our application.

The issuance of a patent is not conclusive as to its inventorship, scope, validity, or enforceability. Our patents may be challenged by third parties and certain of our patents have been challenged. This could result in the patent being deemed invalid, unenforceable or narrowed in scope, or the third party may circumvent any such issued patents. Also, our pending patent applications may not issue, and we may not receive any additional patents.

Our patents or patents we license might not contain claims that are sufficiently broad to prevent others from developing competing products. For instance, issued patents, or patents that may issue in the future, (i) relating to our small molecules may be limited to a particular molecule or molecules and may not cover similar molecules that have similar clinical properties, and (ii) relating to cell or genetic therapies may not cover similar technologies that would allow competitors to achieve similar results. Consequently, our competitors may independently develop competing products that do not infringe our patents or other intellectual property. In addition, CRISPR only has co-exclusive rights to the patent rights that protect the core CRISPR/Cas9 gene-editing technology.

The laws of many foreign jurisdictions do not protect intellectual property rights to the same extent as in the U.S. and many companies in our segment of the pharmaceutical industry have encountered significant difficulties in protecting and defending such rights in foreign jurisdictions. If we encounter such difficulties in protecting or are otherwise precluded from effectively protecting our intellectual property rights in foreign jurisdictions, our business could be substantially harmed.

Because of the extensive time required for the discovery, development, testing and regulatory review of product candidates, it is possible that a patent may expire before a product candidate can be commercialized, or a patent may expire or remain in effect for only a short period following commercialization of such product candidate. This would result in a minimal or non-existent period of patent exclusivity. If our product candidates are not commercialized significantly ahead of the expiration date of any applicable patent, or if we have no patent protection on such product candidates, then, to the extent available we would rely on other forms of exclusivity, such as regulatory exclusivity provided by the FDCA and its counterpart agencies in various jurisdictions, and/or orphan drug exclusivity.

Uncertainty over intellectual property in the pharmaceutical and biotechnology industry has been the source of litigation and other disputes that are inherently costly and unpredictable.

There is considerable uncertainty within our industry about the validity, scope, and enforceability of many issued patents in the U.S. and elsewhere in the world, and, to date, the law and practice remains in substantial flux both in the agencies that grant patents and in the courts. We cannot currently determine the ultimate scope and validity of patents which may be granted to third parties in the future or which patents might be asserted as being infringed by the manufacture, use and sale of our products.

There has been, and we expect that there may continue to be, significant litigation in the pharmaceutical industry regarding patents and other intellectual property rights. Litigation, arbitrations, administrative proceedings, and other legal actions with private parties and governmental authorities concerning patents and other intellectual property rights may be protracted, expensive, and distracting to management. Competitors may sue us as a way of delaying the introduction of our products or to remove our products from the market. Any litigation, including litigation related to Abbreviated New Drug Applications, or ANDA, litigation related to 505(b)(2) applications, interference proceedings to determine priority of

inventions, derivations proceedings, *inter partes* review, oppositions to patents in foreign countries, litigation against our collaborators or similar actions, may be costly and time consuming and could harm our business. We expect that litigation may be necessary in some instances to determine the validity and scope of certain of our proprietary rights. Litigation may be necessary in other instances to determine the validity, scope or non-infringement of certain patent rights claimed by third parties to be pertinent to the manufacture, use or sale of our products. Ultimately, the outcome of such litigation could adversely affect the validity and scope of our patent or other proprietary rights, hinder our ability to manufacture and market our products, or result in the assessment of significant monetary damages against us that may exceed amounts, if any, accrued in our consolidated financial statements.

On July 24, 2020, we filed a lawsuit against Sun Pharmaceutical Industries Limited, or Sun, in the U.S. District Court for the District of Delaware, or the District Court, alleging infringement of U.S. Patent No. 10,646,481, or the ’481 patent. The lawsuit follows Vertex’s receipt of a Notice Letter on June 11, 2020, advising that Sun had submitted an ANDA to the FDA seeking approval to manufacture and market a generic version of the 150 mg tablet of KALYDECO in the U.S. The Notice Letter indicated that Sun submitted a “Paragraph IV” certification to the FDA in which Sun asserted that the ’481 patent is invalid or would not be infringed by Sun’s generic product. The ’481 patent, which expires in 2029, was issued on May 12, 2020, and listed in the Orange Book with respect to KALYDECO 150 mg tablets on June 1, 2020. Sun does not appear to challenge our other U.S. patents covering KALYDECO.

On July 13, 2021, we filed a lawsuit against Lupin Limited and Lupin Pharmaceuticals, Inc., or, collectively, Lupin, in the District Court alleging infringement of the ’481 patent. The lawsuit follows our receipt of a Notice Letter on June 2, 2021 advising that Lupin had submitted an ANDA to the FDA seeking approval to manufacture and market a generic version of the 150 mg tablet of KALYDECO in the U.S. The Notice Letter indicated that Lupin submitted a “Paragraph IV” certification to the FDA in which Lupin asserts that the ’481 patent is invalid or would not be infringed by Lupin’s generic product. Lupin does not appear to challenge our other U.S. patents covering KALYDECO.

On September 24, 2021, the District Court consolidated the cases against Sun and Lupin described above and scheduled trial for the consolidated cases beginning on October 23, 2023. We intend to vigorously enforce its intellectual property rights relating to KALYDECO, including the ’481 patent.

CRISPR has licensed certain rights to a worldwide patent portfolio that covers various aspects of the CRISPR/Cas9 editing platform technology including, for example, compositions of matter and methods of use, including their use in targeting or cutting DNA from Dr. Charpentier, one of the named inventors of this patent portfolio. The patent portfolio also has named inventors who assigned their rights to the CVC Group. For example, in connection with their collaboration, Novartis and Intellia Therapeutics, Inc. have reportedly obtained a license to this patent portfolio in certain fields. Patents and patent applications in this patent portfolio have been the subject of numerous contentious proceedings in the U.S., Europe, and other jurisdictions, including interference proceedings in the USPTO between the CVC Group and (separately) the Broad Institute, Sigma-Aldrich and ToolGen. Decisions rendered to date in these proceedings may be subject to appeal. To date, both the CVC Group and the Broad Institute have obtained granted patents that purport to cover aspects of CRISPR/Cas9 editing platform technology. The patents and patent applications within the patent portfolios of the CVC Group, the Broad Institute, Sigma-Aldrich, and/or ToolGen are, or may in the future be, involved in proceedings similar to interferences or priority disputes in Europe or other foreign jurisdictions. We can give no assurances to the ultimate outcome of these proceedings or the disputes between the CVC Group and the Broad Institute, Sigma-Aldrich and ToolGen.

In addition to the Broad Institute, other third parties have filed patent applications claiming CRISPR/Cas9-related inventions and may allege that they invented one or more of the inventions claimed by the CVC Group. Thus, the USPTO may, in the future, declare an interference between certain CVC Group patent applications and one or more patent applications. The Broad Institute, as well as other third parties, could seek to assert its issued patents against us based on our CRISPR/Cas9-based activities, including commercialization. Defense of these claims, regardless of their merit, could involve substantial litigation expense and could result in a substantial diversion of management and other employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, obtain one or more licenses from third parties, pay royalties or redesign our infringing products, which may be impossible or require substantial time and monetary expenditure. In that event, we could be unable to further develop and commercialize CTX001 or other products that we may develop using the CRISPR/Cas9 technology we license from CRISPR.

To the extent that valid present or future third-party patents or other intellectual property rights cover our products, product candidates or technologies, we or our strategic collaborators may seek licenses or other agreements from the holders of such rights in order to avoid or settle legal claims. Such licenses may not be available on acceptable terms, which may

hinder our ability to, or prevent us from being able to, manufacture and market our products. Payments under any licenses that we are able to obtain would reduce our profits derived from the covered products.

We may be subject to claims by third parties asserting that our employees or we have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Many of our employees were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these employees or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee's former employer. Litigation may be necessary to defend against these claims.

In addition, while it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own. Our and their assignment agreements may not be self-executing or may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property.

If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to management.

Risks Related To Our Operations

Risks associated with operating in foreign countries could materially adversely affect our business.

We have expanded our international operations over the past several years in order to market our CF medicines and expand our research and development capabilities. New laws and industry codes in the E.U. and elsewhere have expanded transparency requirements regarding payments and transfers of value to healthcare professionals, requirements surrounding patient-level clinical trial data, the protection of personal data and increased sanctions for violations. Collectively, our expansion and these new requirements are adding to our compliance costs and potentially exposes us to sanctions in the event of an infringement or failure to report in these jurisdictions. In addition, a significant portion of our commercial supply chain, including sourcing of raw materials and manufacturing, is located in China and the E.U. Consequently, we are, and will continue to be, subject to risks related to operating in foreign countries, including risks relating to intellectual property protections and business interruptions, including as a result of the COVID-19 pandemic. These risks are increased with respect to countries such as China that have substantially different local laws and business practices and weaker protections for intellectual property. Risks associated with operating a global biotechnology company include:

- differing regulatory requirements for drug approvals and regulation of approved drugs in foreign countries;
- varying reimbursement regimes and difficulties or the inability to obtain reimbursement for our products in foreign countries in a timely manner;
- differing patient treatment infrastructures, particularly since our business is focused on the treatment of serious diseases that affect relatively smaller numbers of patients and are typically prescribed by specialist physicians;
- collectability of accounts receivable;
- changes in tariffs, trade barriers, and regulatory requirements, the risks of which appear to have increased in the current political environment;
- economic weakness, including recession and inflation, or political instability in particular foreign economies and markets;
- differing levels of enforcement and/or recognition of contractual and intellectual property rights;
- complying with local laws and regulations, which can change significantly over time;

- foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in reduced revenues or increased operating expenses, and other obligations incident to doing business or operating in another country;
- workforce uncertainty in countries where labor unrest is more common than in the U.S.;
- reliance on third-party vendors and suppliers;
- import and export licensing requirements, tariffs, and other trade and travel restrictions;
- global or regional public health emergencies that could affect our operations or business;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism.

Our revenues are subject to foreign exchange rate fluctuations due to the global nature of our operations. Although we have foreign currency forward contracts to hedge forecasted product revenues denominated in foreign currencies, our efforts to reduce currency exchange losses may not be successful. As a result, currency fluctuations among our reporting currency, the U.S. dollar, and the currencies in which we do business will affect our operating results, often in unpredictable ways.

In addition, our international operations are subject to regulation under U.S. law. For example, the FCPA prohibits U.S. companies and their representatives from offering, promising, authorizing or making payments to foreign officials for the purpose of obtaining or retaining business abroad. In many countries, the health care professionals we regularly interact with may meet the definition of a foreign government official for purposes of the FCPA. We also are subject to import/export control laws. Failure to comply with domestic or foreign laws could result in various adverse consequences, including the possible delay in approval or refusal to approve a product, recalls, seizures, withdrawal of an approved product from the market, the imposition of civil or criminal sanctions, the prosecution of executives overseeing our international operations and corresponding bad publicity and negative perception of our company in foreign countries.

If we fail to attract and retain skilled employees, our business could be materially harmed.

Due to the highly technical nature of our drug discovery and development activities, we require the services of highly qualified and trained scientists who have the skills necessary to conduct these activities. In addition, we need to attract and retain employees with experience in marketing and commercialization of medicines. We have entered into employment agreements with some executives and provide stock-related compensation benefits to all of our key employees that vest over time and therefore induce them to remain with us. However, the employment agreements can be terminated by the executive on relatively short notice. The value to employees of stock-related benefits that vest over time can be significantly affected by movements in our stock price and business performance, and may, at any point in time, be insufficient to counteract more lucrative offers from other companies. We face intense competition for our personnel from our competitors and other companies throughout our industry, especially with respect to employees with expertise in cell or genetic therapies. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. Moreover, the growth of local biotechnology companies and the expansion of major pharmaceutical companies into the Boston area has increased competition for the available pool of skilled employees, especially in technical fields. The high cost of living can make it difficult to attract employees from other parts of the country to our Massachusetts headquarters. Current job market dynamics, caused in part by the effects of COVID-19 and other macro-level events, with many employers unable to fill existing openings at all levels of their organizations, could result in significant increases to our costs to recruit and retain employees. Challenges could adversely affect our operations and financial results if we do not have sufficient staff to perform necessary functions. In addition, the available pool of skilled employees would be further reduced if immigration laws change in a manner that increases restrictions on immigration. Our ability to continue to commercialize our products and achieve our research and development objectives depends on our ability to respond effectively to these demands. If we are unable to hire and retain qualified personnel, there could be a material adverse effect on our business.

We are subject to risks associated with the COVID-19 pandemic.

The COVID-19 pandemic has broadly affected the global economy, resulted in significant travel and work restrictions in

many regions and has put a significant strain on healthcare resources. COVID-19 has had, and we expect it will continue to have, an impact on our operations, an impact on the operations of our collaborators, third-party contractors and other entities, including governments, governmental agencies, and payors, with which we interact, and an impact on the people with CF who take our medicines. In addition, we have seen some delays in enrollment in certain clinical trials, supply chain delays, and regulatory delays due to the COVID-19 pandemic. To date, the most significant effect on our business operations has been the requirement that a majority of our employees work remotely.

We continue to monitor local COVID-19 trends and government guidance for each of our site locations and are utilizing a site-specific approach to assess and permit employee access to our sites. Currently, our sites are open where appropriate and permitted by local laws and guidelines. There can be no assurance that our sites will remain open, when additional employees will gain access to our sites, or whether we will be required to pause or delay enrollment and dosing at clinical trial sites. Any site closure, pause, or delay of a clinical trial could harm our operations and delay the development of our product candidates. In addition, even if sites or clinical trials are open for enrollment, COVID-19 may nevertheless impact clinical trial enrollment or participation, for example due to suspension of in-person procedures required for enrollment, government shut-down orders, or decreased patient willingness to participate compared to pre-COVID-19 pandemic levels. COVID-19 may also impact uptake of our medicines generally and patient retention in clinical trials, potentially resulting in higher drop-out rates or missed visits, which may negatively affect the strength of our clinical trial data.

Health regulatory agencies globally may experience disruptions in their operations as a result of the COVID-19 pandemic. The FDA and comparable foreign regulatory agencies may have slower response times or lack resources to continue to monitor our clinical trials or to engage in other activities related to review of regulatory submissions in drug development. In response to the COVID-19 pandemic and the public health emergency declaration in the U.S., on March 10, 2020, the FDA announced its intention to temporarily postpone most inspections of foreign manufacturing facilities and products, and it subsequently postponed routine surveillance inspections of domestic manufacturing facilities and provided guidance regarding the conduct of clinical trials. In July 2021, the FDA stated that it had begun transitioning back to standard operations for domestic inspections, while continuing to prioritize mission-critical work for foreign inspections. The FDA may not be able to maintain this pace and further delays or setbacks are possible in the future. As a result, review, inspection, and other timelines for our product candidates may be materially delayed for an unknown period of time.

In the future, the economic impacts of the COVID-19 pandemic could affect our business directly or indirectly, including potentially affecting the net prices for our products through changes in our payor mix as a result of increased unemployment in the U.S. or increased pressure on healthcare costs in the U.S. and around the world. The effects on our research, development, manufacturing, and commercialization activities, including the continued launch and uptake of our products, will be dependent on, among other things, the severity and duration of the COVID-19 pandemic and any worsening of the global economic environment as a result thereof, as well as the impact of the pandemic on our third-party manufacturers, suppliers, distributors, subcontractors and customers. While the ultimate impact of COVID-19 on our business is highly uncertain, any negative impacts that materialize could materially adversely affect our operations, financial performance and stock price. Any negative impacts of COVID-19, alone or in combination with others, could exacerbate other risk factors discussed herein. The full extent to which the COVID-19 pandemic will negatively affect our operations, financial performance, and stock price will depend on future developments that are highly uncertain and cannot be predicted, including the scope and duration of the pandemic and actions taken by governmental authorities and other third parties in response to the pandemic.

If we fail to manage our operations effectively, our business may suffer.

We have expanded and are continuing to expand our global operations and capabilities, which has placed, and will continue to place, significant demands on our management and our operational, research and development and financial infrastructure. To effectively manage our business, we need to:

- implement and clearly communicate our corporate-wide strategies;
- enhance our operational and financial infrastructure, including our controls over records and information;
- enhance our operational, financial and management processes, including our cross-functional decision-making processes and our budget prioritization systems;
- train and manage our global employee base; and

- enhance our compliance and legal resources.

Our business faces potential risks relating to the U.K.'s withdrawal from the E.U.

Our European headquarters and European research facility are located in the U.K. On January 31, 2020, the U.K. formally withdrew from the E.U., also known as Brexit. The U.K. and the E.U. negotiated a detailed post-Brexit Trade and Cooperating Agreement which went into effect on January 1, 2021. As of January 1, 2021, E.U. Treaties, E.U. free movement rights and the general principals of E.U. law no longer apply in relation to the U.K. By virtue of the E.U. (Withdrawal) Act 2018, E.U. relations will continue to apply in U.K. domestic law to the extent that they are not modified or revoked by regulations under that Act. Brexit could lead to legal uncertainty and potentially divergent national laws and regulations as the U.K. determines which E.U. laws to replace or replicate. Given the lack of comparable precedent, it is unclear what financial, trade, regulatory and legal implications the withdrawal of the U.K. from the E.U. would have and how such withdrawal would affect us. Any of these effects of Brexit, among others, could adversely affect our business, financial condition and operating results.

Our business has a substantial risk of product liability claims and other litigation liability.

We are or may be involved in various legal proceedings, including securities/shareholder matters and claims related to product liability, intellectual property, employment law, and breach of contract. Such proceedings may involve claims for, or the possibility of, damages or fines and penalties involving substantial amounts of money or other relief, including but not limited to civil or criminal fines and penalties. If any of these legal proceedings were to result in an adverse outcome, it could have a material adverse effect on our business.

With respect to product liability and clinical trial risks, in the ordinary course of business we are subject to liability claims and lawsuits, including potential class actions, alleging that our products or product candidates have caused, or could cause, serious adverse events or other injury. We have product liability insurance and clinical trial insurance in amounts that we believe are adequate to cover this risk. However, our insurance may not provide adequate coverage against all potential liabilities. If a claim is brought against us, we might be required to pay legal and other expenses to defend the claim, as well as pay uncovered damage awards resulting from a claim brought successfully against us and these damages could be significant and have a material adverse effect on our financial condition. Furthermore, whether or not we are ultimately successful in defending any such claims, we might be required to direct significant financial and managerial resources to such defense and adverse publicity is likely to result.

A breakdown or breach of our information technology systems could subject us to liability or interrupt the operation of our business.

We maintain and rely extensively on information technology systems and network infrastructures for the effective operation of our business. In the course of our business, we collect, store, and transmit confidential information (including personal information and intellectual property), and it is critical that we do so in a secure manner to maintain the confidentiality and integrity of such confidential information. A disruption, infiltration, or failure of our information technology systems or any of our data centers as a result of software or hardware malfunctions, computer viruses, cyber-attacks, employee theft or misuse, power disruptions, natural disasters, floods or accidents could cause breaches of data security and loss of critical data, which in turn could materially adversely affect our business and subject us to both private and governmental causes of action. While we have implemented security measures to minimize these risks to our data and information technology systems and have adopted a business continuity plan to deal with a disruption to our information technology systems, there can be no assurance that our efforts to protect our data and information systems will prevent breakdowns or breaches in our systems that could adversely affect our business. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to security breaches, cyber-attacks or other related liabilities.

Cyber-attacks are increasing in their frequency, sophistication, and intensity, and are becoming increasingly difficult to detect. They are often carried out by well-resourced and skilled and parties, including nation states, organized crime groups, "hacktivists" and employees or contractors acting carelessly or with malicious intent. Cyber-attacks include deployment of harmful malware and key loggers, ransomware, denial-of-service attacks, malicious websites, the use of social engineering, and other means to affect the confidentiality, integrity and availability of our technology systems and data. Cyber-attacks also include manufacturing, hardware or software supply chain attacks, which could cause a delay in the manufacturing of products or products produced for contract manufacturing or lead to a data privacy or security breach. Our key business

partners face similar risks, and any security breach of their systems could adversely affect our security posture. In addition, our increased use of cloud technologies heightens these third party and other operational risks, and any failure by cloud or other technology service providers to adequately safeguard their systems and prevent cyber-attacks could disrupt our operations and result in misappropriation, corruption, or loss of confidential or propriety information. Risk of cyber-attack is increased with employees working remotely, including as a result of the ongoing COVID-19 pandemic. During this time, there is an increased risk that we may be vulnerable to cybersecurity-related events such as phishing attacks and other security threats as a result of our employees, third party vendors and collaborators working remotely from non-corporate managed networks.

If our facilities were to experience a catastrophic loss, our operations would be seriously harmed.

Most of our operations, including our research and development activities, are conducted in a limited number of facilities. If any of our major facilities were to experience a catastrophic loss, due to an earthquake, severe storms, fire or similar event, our operations could be seriously harmed. For example, our corporate headquarters, as well as additional leased space that we use for certain logistical and laboratory operations and manufacturing, are located in a flood zone along the Massachusetts coast. We have adopted a business continuity plan to address most crises. However, if we are unable to fully implement our business continuity plans, we may experience delays in recovery of data and/or an inability to perform vital corporate functions, which could result in a significant disruption in our research, development, manufacturing and/or commercial activities, large expenses to repair or replace the facility and/or the loss of critical data, which could have a material adverse effect on our business.

The use of social media platforms presents risks and challenges.

Social media is being used by third parties to communicate about our products and product candidates and the diseases our therapies are designed to treat. We believe that members of the CF community may be more active on social media as compared to other patient populations due to the demographics of this patient population. Social media practices in the pharmaceutical and biotechnology industries are evolving, which creates uncertainty and risk of noncompliance with regulations applicable to our business. For example, patients may use social media platforms to comment on the effectiveness of, or adverse experiences with, a product or a product candidate, which could result in reporting obligations. In addition, our employees may engage on social media in ways that may not comply with legal or regulatory requirements, which may give rise to liability, lead to the loss of trade secrets and other intellectual property, or result in public disclosure of protected personal information. There is a risk of inappropriate disclosure of sensitive information or negative or inaccurate posts or comments about us on any social networking website. Certain data protection regulations, such as the GDPR, apply to personal data contained on social media. If any of these events were to occur or we otherwise fail to comply with applicable regulations, we could incur liability, face regulatory actions or incur harm to our business, including damage to our reputation.

Risks Related to Financial Results and Holding Our Common Stock

Our stock price may fluctuate.

Market prices for securities of companies such as ours are highly volatile. From January 1, 2021 to December 31, 2021, our common stock traded between $176.36 and $242.99 per share. The market for our stock, like that of other companies in the biotechnology industry, has experienced significant price and volume fluctuations. The future market price of our securities could be significantly and adversely affected by factors such as:

- the information contained in our quarterly earnings releases, including updates regarding our commercialized products or our product candidates, our net product revenues and operating expenses for completed periods and guidance regarding future periods;
- announcements of FDA actions with respect to our therapies or those of our competitors, or regulatory filings for our therapies or those of our competitors, or announcements of interim or final results of clinical trials or nonclinical studies relating to our therapies or those of our competitors;
- developments in domestic and international governmental policy or regulation, for example, relating to drug pricing;
- technological innovations or the introduction of new drugs by our competitors;

- government regulatory action;
- public concern as to the safety of drugs developed by us or our competitors;
- developments in patent or other intellectual property rights or announcements relating to these matters;
- information disclosed by third parties regarding our business or products;
- developments relating specifically to other companies and market conditions for pharmaceutical and biotechnology stocks or stocks in general;
- business development, capital structuring or financing activities; and
- general worldwide or national economic, political and capital market conditions, including as a result of the ongoing COVID-19 pandemic.

Following periods of volatility in the market price of a company's securities, stockholder derivative lawsuits and securities class action litigation are common. Such litigation, if instituted against us or our officers and directors, could result in substantial costs and a diversion of management's attention and resources.

Our effective tax rate fluctuates, and changes in tax laws, regulations and treaties, unfavorable resolution of tax contingencies or exposure to additional income tax liabilities could have a material impact on our future taxable income.

Our effective tax rate is derived from a combination of applicable tax rates in the various places that we operate globally. Our effective tax rate may be different than experienced in the past due to numerous factors, including changes in the mix of our profitability from country to country, the results of tax authority examinations/audits of our tax filings, adjustments to the value of our uncertain tax positions, changes in accounting for income taxes, and changes in tax laws or modifications of treaties in various jurisdictions. For example, changes to the U.S. tax code are anticipated under the current administration. Any of these factors could cause us to experience an effective tax rate that is significantly different from previous periods or our current expectations.

We assess the impact of various tax reform proposals and modifications to existing tax treaties in all jurisdictions where we have operations to determine the potential effect on our business and any assumptions we have made about our future taxable income. We cannot predict whether any specific proposals will be enacted, the terms of any such proposals or what effect, if any, such proposals would have on our business if they were to be enacted. Beginning in 2022, the Tax Cuts and Jobs Act of 2017 eliminates the currently available option to deduct research and development expenditures and requires taxpayers to amortize them over five years. The U.S. Congress is considering legislation that would defer the amortization requirement to future periods, however, we have no assurance that the provision will be repealed or otherwise modified. If the requirement is not repealed or modified, it will have a material impact on our cash flows beginning in 2022.

Recommendations from the Organization for Economic Co-operation and Development that are part of the base erosion and profit shifting framework could result in changes in tax laws in jurisdictions in which we do business and adversely affect our provision for income taxes and our current rate. If these recommendations, or other changes in law, were adopted by the jurisdictions in which we do business, it could adversely affect our provision for income tax and our current rate.

We are subject to ongoing tax audits in various jurisdictions, and local tax authorities may disagree with certain positions we have taken and assess additional taxes. We regularly assess the probable outcomes of these audits to determine the appropriateness of our tax provision, and we have established contingency reserves for material tax exposures. However, the calculation of our tax exposures involves the application of complex tax laws and regulations in many jurisdictions, as well as interpretations as to the legality under E.U. state aid rules of tax advantages granted in certain jurisdictions. Therefore, there can be no assurance that we will accurately predict the outcomes of these disputes or other tax audits or that issues raised by tax authorities will be resolved at a financial cost that does not exceed our related reserves and the actual outcomes of these disputes and other tax audits could have a material impact on our results of operations or financial condition.

Our quarterly operating results are subject to significant fluctuation.

Our operating results have fluctuated from quarter to quarter in the past, and we expect that they will continue to do so in the future. Our revenues are primarily dependent on the amount of net product revenues from sales of our CF medicines. Our total net product revenues could vary on a quarterly basis based on, among other factors, the timing of orders from our

significant customers. Additional factors that have caused quarterly fluctuations to our operating results in recent years include variable amounts of revenues, expenses related to business development activities, changes in the fair value of our strategic investments, impairment charges, charges for excess and obsolete inventories, changes in the fair value of derivative instruments and the consolidation or deconsolidation of variable interest entities. Our revenues also are subject to foreign exchange rate fluctuations due to the global nature of our operations. Although we have foreign currency forward contracts to hedge forecasted product revenues denominated in foreign currencies, our efforts to reduce currency exchange losses may not be successful. As a result, currency fluctuations among our reporting currency, the U.S. dollar, and the currencies in which we do business may affect our operating results, often in unpredictable ways. Our quarterly results also could be materially affected by significant charges, which may or may not be similar to charges we have experienced in the past. Most of our operating expenses relate to our research and development activities, do not vary directly with the amount of revenues and are difficult to adjust in the short term. As a result, if revenues in a particular quarter are below expectations, we are unlikely to reduce operating expenses proportionately for that quarter. These examples are only illustrative and other risks, including those discussed in these "Risk Factors," could also cause fluctuations in our reported financial results. Our operating results during any one period do not necessarily suggest the results of future periods.

We expect that results from our clinical development activities and the clinical development activities of our competitors will continue to be released periodically, and may result in significant volatility in the price of our common stock.

Any new information regarding our products and product candidates or competitive products or potentially competitive product candidates can substantially affect investors' perceptions regarding our future prospects. We, our collaborators, and our competitors periodically provide updates regarding drug development programs, typically through press releases, conference calls and presentations at medical conferences. These periodic updates often include interim or final results from clinical trials conducted by us or our competitors and/or information about our or our competitors' expectations regarding regulatory filings and submissions as well as future clinical development of our products or product candidates, competitive products or potentially competitive product candidates. The timing of the release of information by us regarding our drug development programs is often beyond our control and is influenced by the timing of receipt of data from our clinical trials and by the general preference among pharmaceutical companies to disclose clinical data during medical conferences. In addition, the information disclosed about our clinical trials, or our competitors' clinical trials, may be based on interim rather than final data that may involve interpretation difficulties and may in any event not accurately predict final results. The release of such information may result in volatility in the price of our common stock.

General Risk Factors

We may need to raise additional capital that may not be available.

We may need to raise additional capital in the future. Any potential public offering, private placement or debt financing may or may not be similar to the transactions that we entered into in the past. Any debt financing may be on terms that, among other things, include conversion features that could result in dilution to our then-existing security holders and restrict our ability to pay interest and dividends—although we do not intend to pay dividends for the foreseeable future. Any equity financings would result in dilution to our then-existing security holders. If adequate funds are not available on acceptable terms, or at all, we may be required to curtail significantly or discontinue one or more of our research, drug discovery or development programs, including clinical trials, incur significant cash exit costs, or attempt to obtain funds through arrangements with collaborators or others that may require us to relinquish rights to certain of our technologies, products or product candidates. Based on many factors, including general economic conditions, additional financing may not be available on acceptable terms, if at all.

Future indebtedness could materially and adversely affect our financial condition, and the terms of our credit agreements impose restrictions on our business, reducing our operational flexibility and creating default risks.

In 2019, we entered into a credit agreement providing for a $500.0 million revolving facility. In September 2020, we entered into a second credit agreement providing for a $2.0 billion revolving facility. Each of the credit agreements provides that, subject to the satisfaction of certain conditions, we may request the borrowing capacity be increased by an additional $500.0 million. If we borrow under our current credit agreements or any future credit agreement, such indebtedness could have important consequences to our business, including increasing our vulnerability to general adverse financial, business, economic and industry conditions, as well as other factors that are beyond our control. The credit agreements require that we comply with certain financial covenants, including (i) a consolidated leverage ratio covenant and (ii) a consolidated interest coverage ratio covenant, in each case to be measured on a quarterly basis. Further, the credit agreements include negative

covenants, subject to exceptions, restricting or limiting our ability and the ability of our subsidiaries to, among other things, incur additional indebtedness, grant liens, engage in certain investment, acquisition and disposition transactions, pay dividends, repurchase capital stock and enter into transactions with affiliates. As a result, we may be restricted from engaging in business activities that may otherwise improve our business. Failure to comply with the covenants could result in an event of default that could trigger acceleration of our indebtedness, which would require us to repay all amounts owing under the credit agreements and/or our finance leases and could have a material adverse effect on our business. Additionally, our obligations under the credit agreements are unconditionally guaranteed by certain of our domestic subsidiaries.

Issuances of additional shares of our common stock could cause the price of our common stock to decline.

As of December 31, 2021, we had 254.5 million shares of common stock issued and outstanding. As of December 31, 2021, we also had outstanding options to purchase 3.6 million shares of common stock with a weighted-average exercise price of $141.76 per share. Outstanding vested options are likely to be exercised if the market price of our common stock exceeds the applicable exercise price, and, in the future, we expect to issue additional equity awards to directors and employees. In addition, we may issue additional common stock or restricted securities in the future as part of financing activities or business development activities and any such issuances may have a dilutive effect on our then-existing shareholders. Sales of substantial amounts of our common stock in the open market, or the availability of such shares for sale, could adversely affect the price of our common stock. The issuance of restricted common stock or common stock upon exercise of any outstanding options would be dilutive, and may cause the market price for a share of our common stock to decline.

There can be no assurance that we will repurchase shares of common stock or that we will repurchase shares at favorable prices.

In June 2021, our Board of Directors authorized a share repurchase program pursuant to which we are authorized to repurchase up to $1.5 billion of our common stock by December 31, 2022. As of December 31, 2021, we had repurchased $1.0 billion of common stock and had $0.5 billion of remaining authorization for additional share repurchases pursuant to this program.

Our stock repurchases will depend upon, among other factors, our cash balances and potential future capital requirements, results of operations, financial condition, and other factors that we may deem relevant. We can provide no assurance that we will repurchase stock at favorable prices, if at all.

We have adopted anti-takeover provisions and are subject to Massachusetts corporate laws that may frustrate any attempt to remove or replace our current management or effectuate a business combination involving Vertex.

Our corporate charter and by-law provisions and Massachusetts state laws may discourage certain types of transactions involving an actual or potential change of control of Vertex that might be beneficial to us or our security holders. Our by-laws grant the directors a right to adjourn annual meetings of shareholders, and certain provisions of our by-laws may be amended only with an 80% shareholder vote. We may issue shares of any class or series of preferred stock in the future without shareholder approval and upon such terms as our Board of Directors may determine. The rights of the holders of common stock will be subject to, and may be adversely affected by, the rights of the holders of any class or series of preferred stock that may be issued in the future. Massachusetts state law prohibits us from engaging in specified business combinations, unless the combination is approved or consummated in a prescribed manner, and prohibits voting by any shareholder who acquires 20% or more of our voting stock without shareholder approval. As a result, shareholders or other parties may find it more difficult to remove or replace our current management.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, including the descriptions of our Business set forth in Part I, Item 1, our Risk Factors set forth in Part I, Item 1A, and our Management's Discussion and Analysis of Financial Condition and Results of Operations set forth in Part II, Item 7, contains forward-looking statements. Forward-looking statements are not purely historical and may be accompanied by words such as "anticipates," "may," "forecasts," "expects," "intends," "plans," "potentially," "believes," "seeks," "estimates," and other words and terms of similar meaning. Such statements may relate to:

- our expectations regarding the amount of, timing of, and trends with respect to our financial performance, including revenues, costs and expenses, and other gains and losses;

- our expectations regarding clinical trials, including expectations for patient enrollment, development timelines, the expected timing of data from our ongoing and planned clinical trials, and regulatory authority filings and other submissions for our therapies;
- our ability to maintain and obtain adequate reimbursement for our products, our ability to launch, commercialize and market our products or any of our other therapies for which we obtain regulatory approval and our ability to obtain label expansions for existing therapies;
- our expectations regarding our ability to continue to grow our CF business by increasing the number of people with CF eligible and able to receive our medicines and providing improved treatment options for people who are already eligible for one of our medicines;
- the data that will be generated by ongoing and planned clinical trials and the ability to use that data to advance compounds, continue development or support regulatory filings;
- our beliefs regarding the support provided by clinical trials and preclinical and nonclinical studies of our therapies for further investigation, clinical trials or potential use as a treatment;
- our plans to continue investing in our research and development programs, including anticipated timelines for our programs, and our strategy to develop our pipeline programs, alone or with third party-collaborators;
- our beliefs regarding the approximate patient populations for the disease areas on which we focus;
- the potential benefits and therapeutic scope of our acquisitions and collaborations;
- the establishment, development and maintenance of collaborative relationships, including potential milestone payments or other obligations;
- potential business development activities, including the identification of potential collaborative partners or acquisition targets;
- our ability to expand and protect our intellectual property portfolio and otherwise maintain exclusive rights to products;
- potential fluctuations in foreign currency exchange rates and the effectiveness of our foreign currency management program;
- our expectations regarding our provision for or benefit from income taxes and the utilization of our deferred tax assets;
- our ability to use our research programs to identify and develop new product candidates to address serious diseases and significant unmet medical needs;
- our plans to expand, strengthen, and invest in our global supply chains and manufacturing infrastructure and capabilities, including for cell and gene therapies;
- our ability to attract and retain skilled personnel;
- our expectations involving governmental cost containment and other regulatory efforts;
- our expectations surrounding the competitive landscape facing our products and product candidates;
- our expectations regarding the effect of the COVID-19 pandemic on, among other things, our financial performance, liquidity, business and operations, including manufacturing, supply chain, research and development activities and pipeline programs; and
- our liquidity and our expectations regarding the possibility of raising additional capital.

Forward-looking statements are subject to certain risks, uncertainties, or other factors that are difficult to predict and could cause actual events or results to differ materially from those indicated in any such statements. These risks, uncertainties, and other factors include, but are not limited to, those described in our Risk Factors, set forth in Part I, Item 1A, and elsewhere in this report and those described from time to time in our future reports filed with the Securities and Exchange Commission.

Any such forward-looking statements are made on the basis of our views and assumptions as of the date of the filing and are not estimates of future performance. Except as required by law, we undertake no obligation to publicly update any forward-looking statements. The reader is cautioned not to place undue reliance on any such statements.

ITEM 1B. UNRESOLVED STAFF COMMENTS

We did not receive any written comments from the Securities and Exchange Commission prior to the date 180 days before the end of the fiscal year ended December 31, 2021 regarding our filings under the Securities Exchange Act of 1934, as amended, that have not been resolved.

ITEM 2. PROPERTIES

Corporate Headquarters

We lease approximately 1.1 million square feet of office and laboratory space at our corporate headquarters in Boston, Massachusetts in two buildings pursuant to two leases that we entered into in May 2011. These leases commenced in December 2013 and extend until December 2028. We have an option to extend the term of the leases for an additional ten years.

Additional United States and Worldwide Locations

In addition to our corporate headquarters, we lease an aggregate of approximately 728,000 square feet of space globally. This space includes logistical, laboratory, commercial and manufacturing operations, as well as laboratory and office space to support our research and development organizations. We also own approximately 213,000 square feet at our continuous manufacturing facility in Massachusetts.

ITEM 3. LEGAL PROCEEDINGS

We are not currently subject to any material legal proceedings.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

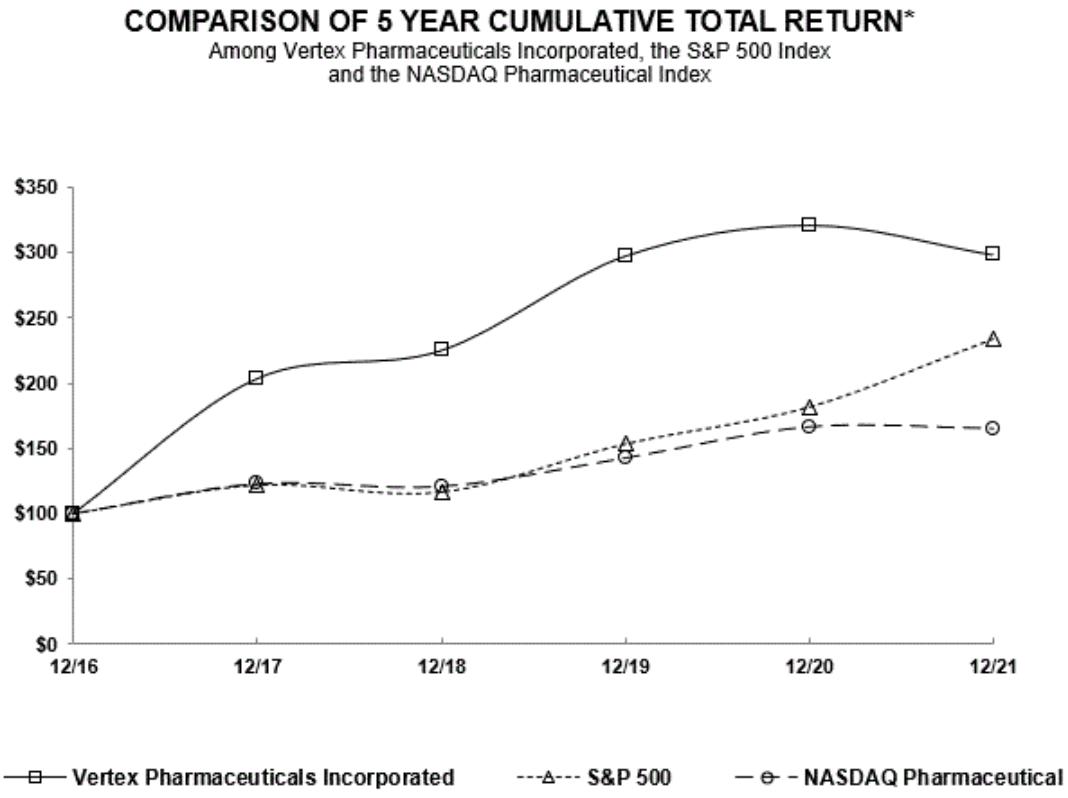
Market Information

Our common stock is traded on The Nasdaq Global Select Market under the symbol "VRTX."

Shareholders

As of January 31, 2022, there were 107 holders of record of our common stock.

Performance Graph



Dividends

We currently expect that any future earnings will be retained for use in our business. Any future determination to declare cash dividends will be subject to the discretion of our board of directors and applicable law and will depend on various factors, including our results of operations, financial condition, prospects and any other factors deemed relevant by our board of directors. In addition, our credit agreement limits our ability to pay cash dividends on our common stock.

Issuer Repurchases of Equity Securities

In June 2021, our board of directors approved a share repurchase program (the "2021 Share Repurchase Program"), pursuant to which we were authorized to repurchase up to $1.5 billion of our common stock by December 31, 2022.

The table set forth below shows repurchases of securities by us during the three months ended December 31, 2021 under our 2021 Share Repurchase Program.

Period	Total Number of Shares Purchased	Average Price Paid per Share	Total Number of Shares Purchased as Part of Publicly Announced Plans or Programs (1)	Approximate dollar value of Shares that May Yet be Purchased Under the Plans or Programs (1)
Oct. 1, 2021 to Oct. 31, 2021	1,984,142	$ 180.33	1,984,142	$ 500,000,086
Nov. 1, 2021 to Nov. 30, 2021	1,900	$ 180.00	1,900	$ 499,658,094
Dec. 1, 2021 to Dec. 31, 2021	—	$ —	—	$ 499,658,094
Total	1,986,042	$ 180.33	1,986,042	$ 499,658,094

(1) Under our 2021 Share Repurchase Program, we are authorized to purchase shares from time to time through open market or privately negotiated transactions. Such purchases may be made pursuant to Rule 10b5-1 plans or other means as determined by our management and in accordance with the requirements of the Securities and Exchange Commission. The approximate dollar value of shares that may yet be repurchased is based solely on shares that may be repurchased under the share repurchase program and excludes any shares that may be repurchased under our employee equity programs.

ITEM 6. [RESERVED]

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

Our discussion and analysis of our financial condition and results of operations for 2021 as compared to 2020 are discussed below. For a discussion of our financial condition and results of operations for 2020 as compared to 2019, please refer to Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations" in our 2020 Annual Report on Form 10-K, except as set forth below.

OVERVIEW

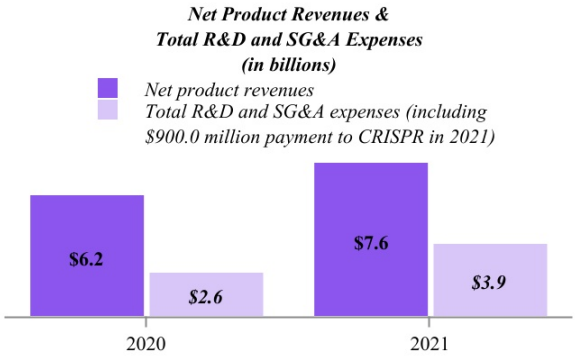
We invest in scientific innovation to create transformative medicines for people with serious diseases with a focus on specialty markets. We have four approved medicines to treat cystic fibrosis, or CF, a life-threatening genetic disease, and are focused on increasing the number of people with CF eligible and able to receive our medicines through label expansions, approval of new medicines and expanded reimbursement. We are broadening our pipeline into additional disease areas through internal research efforts and accessing external innovation through business development transactions.

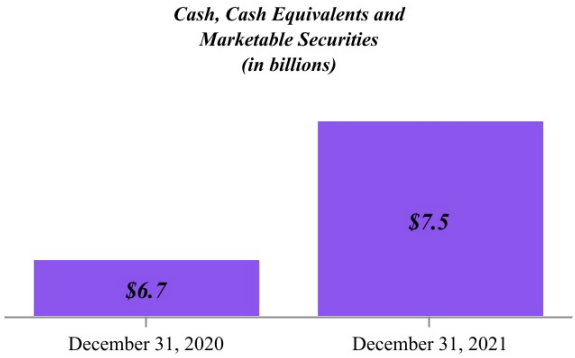
Our triple combination regimen, TRIKAFTA/KAFTRIO was approved in 2019 in the United States, or U.S., and in 2020 in the European Union, or E.U. Collectively, our four medicines are being used by the majority of the approximately 83,000 people with CF in North America, Europe and Australia. We are evaluating our medicines in additional patient populations, including younger children, with the goal of having small molecule treatments for approximately 90% of people with CF.

We continue to research and develop product candidates for the treatment of serious diseases, including genetic therapies to address the remaining approximately 10% of people with CF, sickle cell disease, beta thalassemia, APOL1-mediated kidney disease, type 1 diabetes, pain, alpha-1 antitrypsin deficiency, Duchenne muscular dystrophy, and myotonic dystrophy type 1.

Financial Highlights

Revenues	In 2021, our net product revenues continued to increase due to the uptake of KAFTRIO in Europe and continued strong performance of TRIKAFTA in the U.S., including the expanded indication of TRIKAFTA for children with CF 6 through 11 years of age.
Expenses	Our total R&D and SG&A expenses increased to $3.9 billion as compared to $2.6 billion in 2020 primarily due to a $900.0 million upfront payment we made to CRISPR in connection with an amendment to our CTX001 collaboration. In 2021, cost of sales was 12% of our net product revenues.
Cash	Our cash, cash equivalents and marketable securities increased to $7.5 billion as of December 31, 2021 as compared to $6.7 billion as of December 31, 2020 primarily due to our net product revenues and profitability, offset by repurchases of our common stock and the $900.0 million payment to CRISPR.





Business Updates

Marketed Products

We expect to continue to grow our CF business by increasing the number of people with CF eligible and able to receive our medicines and providing improved treatment options for people who are already eligible for one of our medicines. Since the beginning of 2021, we have made significant progress in activities supporting these efforts.

- The U.S. Food and Drug Administration, or the FDA, approved the use of TRIKAFTA for children with CF 6 through 11 years of age who have at least one F508del mutation or at least one mutation that is responsive to TRIKAFTA.
- In January 2022, the European Commission and the U.K.'s Medicines and Healthcare products Regulatory Agency granted marketing authorization for KAFTRIO in the treatment of children with CF 6 through 11 years of age who have at least one F508del mutation in the CFTR gene.
- TRIKAFTA/KAFTRIO is now approved and reimbursed or accessible in more than 20 countries outside the U.S.
- Our Phase 3 clinical trial evaluating ORKAMBI for the treatment of children with CF 12 through 24 months of age met its primary endpoint. Based on these data, we plan to submit regulatory filings in the U.S. and Europe in the first and second quarters of 2022, respectively.

Pipeline

We continue to advance a pipeline of potentially transformative small molecule, and cell and genetic therapies aimed at treating serious diseases. Since the beginning of 2021, we have made important progress in activities supporting these programs.

Cystic Fibrosis

- In the third quarter of 2021, we announced the initiation of Phase 3 clinical trials evaluating a once-daily investigational triple combination of VX-121/tezacaftor/VX-561 (deutivacaftor). Enrollment is underway in these two Phase 3 clinical trials, and we expect to complete enrollment in both trials by late 2022 or early 2023.
- We are conducting enabling studies for CF messenger ribonucleic acid, or mRNA, therapeutics designed to treat the underlying cause of CF by enabling cells in the lungs to produce functional CFTR protein for the treatment of the approximately 10% of people with CF who do not produce any CFTR protein. We expect to submit an Investigational New Drug Application, or IND, for this program in 2022.

Sickle Cell Disease and Beta Thalassemia

- We are evaluating the use of a non-viral ex vivo CRISPR gene-editing therapy, CTX001, for the treatment of severe sickle cell disease, or SCD, and transfusion-dependent beta thalassemia, or TDT. Enrollment is complete in the ongoing clinical trials evaluating CTX001 in severe SCD and TDT.
- Data presented to date support the profile of CTX001 as a potential one-time functional cure for people with severe SCD and TDT. CTX001 safety data to date is generally consistent with an autologous stem cell transplant and myeloablative conditioning. We anticipate regulatory submissions of CTX001 in late 2022.

APOL1-Mediated Kidney Disease

- In December 2021, we announced that patients with APOL1-mediated focal segmental glomerulosclerosis, or FSGS, treated with VX-147, a small molecule inhibitor of APOL1 function, on top of standard of care achieved a statistically significant, substantial and clinically meaningful reduction of proteinuria in a Phase 2 proof-of-concept clinical trial. We anticipate completing our end of Phase 2 meetings with regulators and advancing VX-147 into pivotal development in people with APOL1-mediated kidney disease, or AMKD, including APOL1-mediated FSGS, in the first quarter of 2022.

Type 1 Diabetes

- VX-880 is a stem cell-derived, allogeneic, fully differentiated, insulin-secreting islet cell replacement therapy, using standard immunosuppression to protect the implanted cells. Our Phase 1/2 clinical trial evaluating VX-880 as a potential treatment for type 1 diabetes, or T1D, is ongoing at multiple clinical sites in the U.S. In January 2022, we announced positive Day 150 data for the first T1D patient in this clinical trial, including restoration of islet cell function and rapid improvements in multiple measures. In this first patient, the safety of VX-880 was generally consistent with the immunosuppressive regimen used in this study. We will continue to dose patients in 2022.
- We also are pursuing additional programs in T1D, in which these stem cell-derived, fully differentiated, insulin-secreting islet cells are encapsulated and implanted in an immunoprotective device or modified to produce hypoimmune cells. We are conducting IND-enabling studies for the cells and device program, and we expect to submit an Investigational New Drug Application, or IND, for this program in 2022.

Pain

- Two Phase 2 dose ranging acute pain clinical trials evaluating VX-548, a selective small molecule inhibitor of NaV1.8, are underway; one following bunionectomy surgery and the other following abdominoplasty surgery. We expect to obtain data from the clinical trials evaluating VX-548 in the first quarter of 2022.

Alpha-1 Antitrypsin, or AAT, Deficiency

- We plan to advance one or more novel small molecule Z-AAT correctors into the clinic in 2022.

Investments in External Innovation

- Pursuant to a collaboration with CRISPR that we amended in 2021, we now lead global development, manufacturing and commercialization of CTX001, with support from CRISPR.
- We entered into research collaborations with Obsidian Therapeutics, Inc., Arbor Biotechnologies, Inc., and Mammoth Biosciences, Inc.

Our Business Environment

Our net product revenues come from the sale of our medicines for the treatment of CF. Our CF strategy involves continuing to develop and obtain approval and reimbursement for treatment regimens that will provide benefits to all people with CF and increasing the number of people with CF eligible and able to receive our medicines, including through label expansions, expanded reimbursement, and the development of new medicines. We are actively pursuing a pipeline of product candidates for the treatment of serious diseases outside of CF. Our strategy is to combine transformative advances in the understanding of human disease biology and the science of therapeutics in order to discover and develop new medicines. This approach includes advancing multiple compounds from each program, spanning multiple modalities, into early clinical trials and evaluating patient data to inform discovery and development of additional compounds, with the goal of bringing first-in-class and best-in-class therapies to patients, and to provide durable clinical and commercial success.

In pursuit of new product candidates and therapies in specialty markets, we invest in research and development. We believe that pursuing research in diverse areas allows us to balance the risks inherent in product development and may provide product candidates that will form our pipeline in future years. To supplement our internal research programs, we acquire technologies and programs and collaborate with biopharmaceutical and technology companies, leading academic research institutions, government laboratories, foundations and other organizations, as needed, to advance research in our areas of therapeutic interest and to access technologies needed to execute on our strategy.

Discovery and development of a new pharmaceutical or biological product is a difficult and lengthy process that requires significant financial resources along with extensive technical and regulatory expertise. Most chemical compounds that are investigated as potential drug or biological product candidates never progress into development, and most product candidates that do advance into development never receive marketing approval. Our investments in product candidates are subject to considerable risks. We closely monitor the results of our discovery, research, clinical trials and nonclinical studies and frequently evaluate our product development programs in light of new data and scientific, business and commercial insights, with the objective of balancing risk and potential. This process can result in rapid changes in focus and priorities as new

information becomes available and as we gain additional understanding of our ongoing programs and potential new programs, as well as those of our competitors.

Our business also requires ensuring appropriate manufacturing and reimbursement of our products. As we advance our product candidates through clinical development toward commercialization and market and sell our approved products, we build and maintain our supply chain and quality assurance resources. We rely on a global network of third parties and our internal capabilities to manufacture and distribute our products for commercial sale and post-approval clinical trials and to manufacture and distribute our product candidates for clinical trials. In addition to establishing supply chains for each new approved product, we adapt our supply chain for existing products to include additional formulations or to increase scale of production for existing products as needed. The processes for cell and genetic therapies can be more complex than those required for small molecule drugs and require different systems, equipment, facilities and expertise. We are focused on ensuring the stability of the supply chains for our current products, as well as for our pipeline programs.

Sales of our products depend, to a large degree, on the extent to which our products are reimbursed by third-party payors, such as government health programs, commercial insurance and managed health care organizations. Reimbursement for our products, including our potential pipeline therapies, cannot be assured and may take significant periods of time to obtain. We dedicate substantial management and other resources in order to obtain and maintain appropriate levels of reimbursement for our products from third-party payors, including governmental organizations, in the U.S. and ex-U.S. markets.

In the U.S., we have worked successfully with third-party payors in order to promptly obtain appropriate levels of reimbursement for our CF medicines. We plan to continue to engage in discussions with numerous commercial insurers and managed health care organizations, along with government health programs that are typically managed by authorities in the individual states, to ensure that payors recognize the significant benefits that our medicines provide and provide patients with appropriate levels of access to our medicines now and in the future. In Europe and other ex-U.S. markets, we seek government reimbursement for our medicines on a country-by-country or region-by-region basis, as required. This is necessary for each new medicine, as well as for label expansions for our current medicines. We expect to continue to focus significant resources to obtain expanded reimbursement for our CF medicines and, ultimately, pipeline therapies in U.S. and ex-U.S. markets.

COVID-19

We continue to monitor the impacts of the COVID-19 global pandemic on our business, including in our clinical trials, manufacturing facilities and capabilities, and ability to access necessary resources. COVID-19 has not materially affected our supply chain or the demand for our medicines, and we believe that we will be able to continue to supply all of our approved medicines to patients globally. We adjusted our business operations in response to COVID-19 and have continued to monitor local COVID-19 trends and government guidance for each of our site locations. We are utilizing a site-specific approach to assess and permit employee access to our sites. Currently, our sites are open to certain employees where appropriate and permitted by local laws and guidelines.

Strategic Transactions

Acquisitions

As part of our business strategy, we seek to acquire products, product candidates and other technologies and businesses that are aligned with our corporate and research and development strategies and complement and advance our ongoing research and development efforts. In 2019, we invested significantly in business development transactions designed to augment our pipeline, including the acquisition of Semma Therapeutics, Inc., or Semma, a privately-held company focused on the use of stem cell-derived human islets as a treatment for T1D, and Exonics Therapeutics, Inc., or Exonics, a privately-held company focused on creating transformative gene-editing therapies to repair mutations that cause Duchenne muscular dystrophy, or DMD, and other severe neuromuscular diseases, including myotonic dystrophy type 1, or DM1. In the Semma acquisition, we paid approximately $950.0 million in cash to Semma equity holders. In the Exonics acquisition, we paid approximately $245.0 million upfront to Exonics equity holders and agreed to additional payments based upon successful achievement of specified development and regulatory milestones. We expect to continue to identify and evaluate potential acquisitions and may include larger transactions or later-stage assets.

Both of our 2019 acquisitions were accounted for as business combinations. As of the acquisition date for each transaction, the cash payments, as well as the fair value of contingent consideration for Exonics, were allocated primarily to

goodwill and the fair value of several in-process research and development assets that we acquired. The fair value of contingent consideration related to Exonics was recorded as a liability and continues to be adjusted on a quarterly basis. As a result, these acquisitions are primarily reflected in additional assets and liabilities on our consolidated balance sheet. Operating expenses incurred by Exonics and Semma after the acquisition dates and specific expenses associated with the acquisitions are reflected in our consolidated statement of operations.

Please refer to our critical accounting policies, "Acquisitions," for further information regarding the significant judgments and estimates related to our acquisitions.

Collaboration and Licensing Arrangements

We enter into arrangements with third parties, including collaboration and licensing arrangements, for the development, manufacture and commercialization of products, product candidates, and other technologies that have the potential to complement our ongoing research and development efforts. We expect to continue to identify and evaluate collaboration and licensing opportunities that may be similar to or different from the collaborations and licenses that we have engaged in previously.

In-License Agreements

We have entered into collaborations with biotechnology and pharmaceutical companies in order to acquire rights or to license product candidates or technologies that enhance our pipeline and/or our research capabilities. Over the last several years, we entered into collaboration agreements with a number of companies, including Arbor Biotechnologies, Inc., CRISPR, Kymera Therapeutics, Inc., Mammoth Biosciences, Inc., Moderna, Inc., and Obsidian Therapeutics, Inc. Generally, when we in-license a technology or product candidate, we make upfront payments to the collaborator, assume the costs of the program, and/or agree to make contingent payments, which could consist of milestone, royalty, and option payments. Most of these collaboration payments are expensed as research and development expenses; however, depending on many factors, including the structure of the collaboration, the significance of the in-licensed product candidate to the collaborator's operations and the other activities in which our collaborators are engaged, the accounting for these transactions can vary significantly. Our research and development expenses included $1.1 billion in 2021, $184.6 million in 2020 and $318.3 million in 2019 related to upfront, milestone and other payments pursuant to our collaboration agreements and other business development agreements. The increase in these payments in 2021 was primarily related to the $900.0 million upfront payment we made to CRISPR that is described below.

Joint Development and Commercialization Agreement with CRISPR

In 2017, we entered into a joint development and commercialization agreement, or the Original JDCA, with CRISPR pursuant to which we are developing and preparing to commercialize CTX001 for TDT and SCD. The Original JDCA was entered into following our exercise of an option to co-develop and co-commercialize the hemoglobinopathies program that was contained in a collaboration agreement that we entered into with CRISPR in 2015.

In April 2021, we and CRISPR entered into an amendment and restatement of the Original JDCA, or the A&R JDCA. In June 2021, we made a $900.0 million upfront payment to CRISPR in connection with the closing of the transactions contemplated by the A&R JDCA. We concluded that we did not have any alternative future use for the acquired in-process research and development and recorded this upfront payment to "Research and development expenses." Under the terms of the A&R JDCA, we are leading worldwide development, manufacturing, and commercialization of CTX001. As of July 1, 2021, 60% of the net profits and net losses for CTX001 are allocated to us and 40% of the net profits and net losses for CTX001 are allocated to CRISPR. CRISPR may earn an additional one-time $200.0 million milestone payment upon regulatory approval of CTX001. We concluded that the Original JDCA and the A&R JDCA are cost-sharing arrangements, which result in the net impact of the arrangements being recorded in "Research and development expenses" in our consolidated statements of operations.

Out-License Agreements

We also have out-licensed internally-developed programs to collaborators who are leading the development of these programs. These out-license arrangements include our agreement with Merck KGaA, Darmstadt, Germany, which licensed oncology research and development programs from us in early 2017. Pursuant to these out-licensing arrangements, our collaborators are responsible for the research, development, and commercialization costs associated with these programs, and we are entitled to receive contingent milestone and/or royalty payments. As a result, we do not expect to incur significant

expenses in connection with these programs and have the potential for future collaborative and royalty revenues resulting from these programs.

Please refer to Note B, “Collaborative and Other Arrangements,” for further information regarding our in-license agreements and out-license agreements.

Strategic Investments

In connection with our business development activities, we have periodically made equity investments in our collaborators. As of December 31, 2021, we held strategic equity investments in certain public and private companies, and we expect to make additional strategic equity investments in the future. While we invest the majority of our cash, cash equivalents, and marketable securities in instruments that meet specific credit quality standards and limit our exposure to any one issue or type of instrument, our strategic investments are maintained and managed separately from our other cash, cash equivalents, and marketable securities. As discussed below in “Other Income (Expense), Net” in our *Results of Operations*, any changes in the fair value of equity investments with readily determinable fair values (including publicly traded securities) are recorded to other income (expense), net in our consolidated statement of operations.

RESULTS OF OPERATIONS

	2021	% Change	2020	% Change	2019
	(in millions, except percentages and per share amounts)				
Revenues	$ 7,574.4	22%	$ 6,205.7	49%	$ 4,162.8
Operating costs and expenses	4,792.3	43%	3,349.4	13%	2,965.3
Income from operations	2,782.1	(3)%	2,856.3	139%	1,197.5
Other non-operating (expense) income, net	(51.7)	**	260.6	32%	197.4
Provision for income taxes	388.3	(4)%	405.2	86%	218.1
Net income	$ 2,342.1	(14)%	$ 2,711.7	130%	$ 1,176.8
Net income per diluted common share	$ 9.01		$ 10.29		$ 4.51
Diluted shares used in per share calculations	259.9		263.4		260.7

** Not meaningful

Revenues

	2021	% Change	2020	% Change	2019
	(in millions, except percentages)				
TRIKAFTA/KAFTRIO	$ 5,697.2	47%	$ 3,863.8	820%	$ 420.1
SYMDEKO/SYMKEVI	420.4	(33)%	628.6	(56)%	1,417.7
ORKAMBI	771.6	(15)%	907.5	(32)%	1,331.9
KALYDECO	684.2	(15)%	802.9	(19)%	991.0
Product revenues, net	7,573.4	22%	6,202.8	49%	4,160.7
Other revenues	1.0	**	2.9	**	2.1
Total revenues	$ 7,574.4	22%	$ 6,205.7	49%	$ 4,162.8

** Not meaningful

Product Revenues, Net

In 2021, our net product revenues increased by $1.4 billion, or 22%, as compared to 2020 primarily due to the launch of KAFTRIO in multiple countries internationally, which was approved in the E.U. in the third quarter of 2020, and the performance of TRIKAFTA in the U.S., including the launch of TRIKAFTA in June 2021 for children with CF 6 through 11 years of age. Decreases in revenues for our products other than TRIKAFTA/KAFTRIO were primarily the result of patients switching from these medicines to TRIKAFTA/KAFTRIO.

Our net product revenues from the U.S. and from ex-U.S. markets were as follows:

	2021	% Change	2020	% Change	2019
	(in millions, except percentages)				
United States	$ 5,287.3	10%	$ 4,826.4	58%	$ 3,060.3
ex-U.S.	2,286.1	66%	1,376.4	25%	1,100.4
Product revenues, net	$ 7,573.4	22%	$ 6,202.8	49%	$ 4,160.7

We expect that our net product revenues will increase in 2022 due to increasing numbers of people being treated with our medicines. The increase is expected to result from continued performance of KAFTRIO outside the U.S. and TRIKAFTA in the U.S., label expansions for our previously approved products, and expanded access to our medicines.

Other Revenues

Our other revenues were $1.0 million and $2.9 million in 2021 and 2020, respectively, related to collaborative milestones that we earned. Our other revenues have historically fluctuated significantly from one period to another based on our collaborative out-license activities, and may continue to fluctuate in the future.

Operating Costs and Expenses

	2021	% Change	2020	% Change	2019
	(in millions, except percentages)				
Cost of sales	$ 904.2	23%	$ 736.3	34%	$ 547.8
Research and development expenses	3,051.1	67%	1,829.5	4%	1,754.5
Selling, general and administrative expenses	840.1	9%	770.5	17%	658.5
Change in fair value of contingent consideration	(3.1)	**	13.1	**	4.5
Total costs and expenses	$ 4,792.3	43%	$ 3,349.4	13%	$ 2,965.3

** Not meaningful

Cost of Sales

Our cost of sales primarily consists of third-party royalties payable on net sales of our products as well as the cost of producing inventories. Pursuant to our agreement with the Cystic Fibrosis Foundation, our tiered third-party royalties on sales of TRIKAFTA/KAFTRIO, SYMDEKO/SYMKEVI, KALYDECO, and ORKAMBI, calculated as a percentage of net sales, range from the single digits to the sub-teens, with royalties on sales of TRIKAFTA/KAFTRIO slightly lower than for our other products. Over the last several years, our cost of sales has been increasing due to increased net product revenues. Our cost of sales as a percentage of our net product revenues was 12% in each of 2021 and 2020. In 2022, we expect our total cost of sales will increase due to expected increases in our net product revenues and our cost of sales as a percentage of our net product revenues will be similar to our cost of sales as a percentage of net product revenues in 2021 and 2020.

Research and Development Expenses

	2021	% Change	2020	% Change	2019
	(in millions, except percentages)				
Research expenses	$ 617.7	(3)%	$ 636.7	(13)%	$ 732.7
Development expenses	2,433.4	104%	1,192.8	17%	1,021.8
Total research and development expenses	$ 3,051.1	67%	$ 1,829.5	4%	$ 1,754.5

Our research and development expenses include internal and external costs incurred for research and development of our products and product candidates and expenses related to certain technologies that we acquire or license through business development transactions. We do not assign our internal costs, such as salary and benefits, stock-based compensation expense, laboratory supplies and other direct expenses and infrastructure costs, to individual products or product candidates, because the employees within our research and development groups typically are deployed across multiple research and development programs. We assign external costs of services provided to us by clinical research organizations and other outsourced research by individual program. Apart from upfront, milestone, and other payments related to our business development activities, our internal costs are significantly greater than our external costs. All research and development costs for our products and product candidates are expensed as incurred.

Over the past three years, we have incurred $6.6 billion in research and development expenses associated with product discovery and development. The successful development of our product candidates is highly uncertain and subject to a number of risks. In addition, the duration of clinical trials may vary substantially according to the type, complexity and novelty of the product candidate and the disease indication being targeted. The FDA and comparable agencies in foreign countries impose substantial requirements on the introduction of therapeutic pharmaceutical products, typically requiring lengthy and detailed laboratory and clinical testing procedures, sampling activities and other costly and time-consuming procedures. Data obtained from nonclinical and clinical activities at any step in the testing process may be adverse and lead to discontinuation or redirection of development activities. Data obtained from these activities also are susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The duration and cost of discovery, nonclinical

studies and clinical trials may vary significantly over the life of a project and are difficult to predict. Therefore, accurate and meaningful estimates of the ultimate costs to bring our product candidates to market are not available. Any estimates regarding development and regulatory timelines for our product candidates are highly subjective and subject to change. Until we have data from Phase 3 clinical trials, we cannot make a meaningful estimate regarding when, or if, a clinical development program will generate revenues and cash flows.

Research Expenses

	2021	Change %	2020	Change %	2019
	(in millions, except percentages)				
Research Expenses:					
Salary and benefits	$ 136.7	5%	$ 129.8	(4)%	$ 134.6
Stock-based compensation expense	77.3	(10)%	85.6	23%	69.4
Outsourced services and other direct expenses	160.0	38%	116.2	—%	116.6
Collaborative payments	105.4	(43)%	184.6	(40)%	307.8
Infrastructure costs	138.3	15%	120.5	16%	104.3
Total research expenses	$ 617.7	(3)%	$ 636.7	(13)%	$ 732.7

We expect to continue to invest in our research programs with a focus on creating transformative medicines for serious diseases. Our research expenses have historically fluctuated, and are expected to continue to fluctuate, from one period to another due to upfront, milestone and certain other payments related to our business development activities that are reflected in the preceding table as collaborative payments. Our research expenses, apart from these collaborative payments, have been increasing over the last several years as we have invested in our pipeline and expanded our cell and genetic therapy capabilities.

Development Expenses

	2021	Change %	2020	Change %	2019
	(in millions, except percentages)				
Development Expenses:					
Salary and benefits	$ 347.6	18%	$ 295.7	18%	$ 249.9
Stock-based compensation expense	191.0	8%	177.1	14%	155.2
Outsourced services and other direct expenses	629.4	23%	512.2	21%	425.0
Collaborative payments	1,007.9	**	—	**	10.5
Infrastructure costs	257.5	24%	207.8	15%	181.2
Total development expenses	$ 2,433.4	104%	$ 1,192.8	17%	$ 1,021.8

** Not meaningful

In 2021 and 2020, costs related to our CF programs represented the largest portion of our development costs, apart from the $900.0 million upfront payment to CRISPR in 2021, which is included in the preceding table under collaborative payments. Our development expenses increased by $1.2 billion, or 104%, in 2021 as compared to 2020, primarily due to the payment to CRISPR and increased expenses related to our diversifying pipeline, including clinical trials, headcount, and infrastructure costs. We expect our development expenses, apart from payments related to our business development activities, to continue to increase in 2022 as a result of our diversifying pipeline.

Selling, General and Administrative Expenses

	2021	% Change	2020	% Change	2019
	(in millions, except percentages)				
Selling, general and administrative expenses	$ 840.1	9%	$ 770.5	17%	$ 658.5

Selling, general and administrative expenses increased by 9% in 2021 as compared to 2020, primarily due to the continued investment to support the commercialization of our medicines and increased support for our pipeline products. We expect our selling, general and administrative expenses to continue to increase in 2022.

Contingent Consideration

The change in the fair value of our contingent consideration potentially payable to Exonics' former equity holders was a $3.1 million decrease in 2021 and a $13.1 million increase in 2020. In future periods, we expect the fair value of contingent consideration to increase or decrease based on, among other things, our estimates of the probability of achieving and the timing of these contingent development and regulatory milestone payments, as well as the time value of money and changes in market interest rates.

Other Non-Operating Income (Expense), Net

Interest Income

Interest income was $4.9 million in 2021, which was lower than our interest income of $22.2 million in 2020, due to a decrease in prevailing market interest rates, despite an increase in our cash equivalents and available-for-sale debt securities. Our future interest income will be dependent on the amount of, and prevailing market interest rates on, our outstanding cash equivalents and available-for-sale debt securities.

Interest Expense

Interest expense was $61.5 million in 2021 as compared to $58.2 million in 2020. The majority of our interest expense in these periods was related to imputed interest expense associated with our leased corporate headquarters in Boston.

Other Income (Expense), Net

In 2021 and 2020, we recorded net other income of $4.9 million and $296.6 million, respectively, primarily related to net gains of $17.1 million and $311.9 million in 2021 and 2020, respectively, resulting from changes in the fair value and sales of certain of our strategic investments. As of December 31, 2021, the fair value of our investments in publicly traded companies was $230.9 million. To the extent that we continue to hold strategic investments, particularly strategic investments in publicly traded companies, we will record other income (expense) related to these strategic investments on a quarterly basis. We expect that due to the volatility of the stock price of biotechnology companies, our other income (expense), net will fluctuate in future periods based on increases or decreases in the fair value of our strategic investments.

Income Taxes

Our provision for income taxes was $388.3 million for 2021 and $405.2 million for 2020. Our effective tax rate of 14% for 2021 was lower than the U.S. statutory rate primarily due to discrete tax benefits of (i) $94.8 million associated with an increase in the U.K.'s corporate tax rate from 19% to 25%, which was enacted in June 2021 and will become effective in April 2023, and (ii) $44.1 million resulting from an R&D tax credit study that we completed in 2021.

Our effective tax rate of 13% for 2020 was lower than the U.S. statutory rate primarily due to (i) a discrete tax benefit of $209.0 million associated with the transfer of intellectual property rights to the U.K., (ii) a discrete tax benefit associated with the write-off of a long-term intercompany receivable, (iii) a discrete tax benefit associated with an increase in the U.K.'s corporate tax rate from 17% to 19%, which was enacted and became effective in July 2020, and (iv) excess tax benefits related to stock-based compensation. The impact of these items was partially offset by U.S. income tax on foreign earnings.

Net Income

In summary, our net income decreased to $2.3 billion in 2021 as compared to $2.7 billion in 2020 primarily due to (i) our $900.0 million upfront payment to CRISPR in 2021 and (ii) less other income derived from changes in the fair value of our strategic investments in 2021 as compared to 2020, (iii) partially offset by increased operating income in 2021, apart from the payment to CRISPR, resulting from our product revenues.

LIQUIDITY AND CAPITAL RESOURCES

The following table summarizes the components of our financial condition as of December 31, 2021 and 2020:

	2021	2020	% Change
	(in millions)		
Cash, cash equivalents and marketable securities	$ 7,524.9	$ 6,658.9	13%
Working Capital:			
Total current assets	$ 9,560.6	$ 8,133.4	18%
Total current liabilities	(2,142.0)	(1,877.5)	14%
Total working capital	$ 7,418.6	$ 6,255.9	19%

Working Capital

As of December 31, 2021, total working capital was $7.4 billion, which represented an increase of $1.2 billion from $6.3 billion as of December 31, 2020. The increase in total working capital in 2021 was primarily related to $2.6 billion of cash provided by operations, which was net of our $900.0 million payment to CRISPR, partially offset by $1.4 billion of cash used to repurchase our common stock pursuant to our share repurchase programs and purchases of property and equipment of $235.0 million.

Sources and Uses of Liquidity

As of December 31, 2021, we had cash, cash equivalents, and marketable securities of $7.5 billion, which represented an increase of $866.0 million from $6.7 billion as of December 31, 2020. We intend to rely on our existing cash, cash equivalents and marketable securities together with cash flows from product sales as our primary source of liquidity.

We expect that cash flows from our products together with our current cash, cash equivalents and marketable securities will be sufficient to fund our operations for at least the next twelve months. The adequacy of our available funds to meet our future operating and capital requirements will depend on many factors, including the amounts of future revenues generated by our products, and the potential introduction of one or more of our other product candidates to the market, the level of our business development activities and the number, breadth, cost and prospects of our research and development programs.

Credit Facilities & Financing Strategy

We may borrow up to a total of $2.5 billion pursuant to two revolving credit facilities. We may repay and reborrow amounts under these revolving credit agreements without penalty. Subject to certain conditions, we may request that the borrowing capacity for each of the credit agreements be increased by an additional $500.0 million, for a total of $3.5 billion collectively. Negative covenants in our credit agreement may prohibit or limit our ability to access these sources of liquidity. As of December 31, 2021, we were in compliance with these covenants.

We may also raise additional capital by borrowing under credit agreements, through public offerings or private placements of our securities or securing new collaborative agreements or other methods of financing. We will continue to manage our capital structure and will consider all financing opportunities, whenever they may occur, that could strengthen our long-term liquidity profile. There can be no assurance that any such financing opportunities will be available on acceptable terms, if at all.

Cash Flows

	2021	2020	2019
		(in millions)	
Net cash provided by (used in):			
Operating activities	$ 2,643.5	$ 3,253.5	$ 1,569.3
Investing activities	$ (340.9)	$ 99.4	$ (1,235.3)
Financing activities	$ (1,478.0)	$ (505.3)	$ 126.8

Operating Activities

Cash provided by operating activities was $2.6 billion in 2021 as compared to $3.3 billion in 2020 primarily due to a $369.6 million decrease in our net income resulting from the $900.0 million upfront payment we made to CRISPR in 2021. Cash provided by operating activities was $3.3 billion in 2020 as compared to $1.6 billion in 2019 primarily due to a $1.5 billion increase in our net income resulting from increased net product revenues.

Investing Activities

Cash used in investing activities was $340.9 million in 2021, primarily related to purchases of property and equipment, and, to a lesser extent, purchases of notes receivable and strategic investments. In 2020, our investing activities primarily related to $437.6 million of proceeds from sales of our strategic investments, partially offset by purchases of property and equipment. In 2019, we spent $1.2 billion to acquire Semma and Exonics.

Financing Activities

Cash used in financing activities was $1.5 billion in 2021 and $505.3 million in 2020 as compared to cash provided by financing activities of $126.8 million in 2019. In 2021 and 2020, aggregate share repurchases pursuant to our share repurchase programs were $1.4 billion and $539.1 million, respectively, which represented the largest portion of our financing activities. In 2019, our financing activities provided $126.8 million of cash related to the issuance of common stock pursuant to our employee benefit plans, partially offset by repurchases of our common stock pursuant to our share repurchase programs.

Future Capital Requirements

We have significant future capital requirements including:

- significant expected operating expenses to conduct research and development activities and to operate our organization;
- substantial facility and finance lease obligations as described below;
- royalties we pay to the Cystic Fibrosis Foundation on sales of our CF products; and
- cash paid for income taxes.

In addition, we have significant potential future capital requirements including:

- We have entered into certain collaboration agreements with third parties that include the funding of certain research, development, and commercialization efforts. Certain of our business development transactions, including collaborations and acquisitions, include the potential for future milestone and royalty payments by us upon the achievement of pre-established developmental and regulatory targets and/or commercial targets. Our obligation to fund these research and development and commercialization efforts and to pay these potential milestone and royalties is contingent upon continued involvement in the programs and/or the lack of any adverse events that could cause the discontinuance of the programs associated with our collaborations and acquisitions. We may enter into additional business development transactions, including acquisitions, collaborations, and equity investments, that require additional capital.

- To the extent we borrow amounts under our existing credit agreements, we would be required to repay any outstanding principal amounts in 2022 or 2024.
- As of December 31, 2021, we had $0.5 billion available under our 2021 Share Repurchase Program.

Additional information on several of our future capital requirements is provided below.

Research and Development Costs

At any point in time, we have several ongoing clinical trials at various stages of clinical development. Our clinical trial costs are dependent on, among other things, our research activities advancing to later-stage clinical development as well as the size, number, and length of our clinical trials.

Leases

Finance Leases

Our corporate headquarters is in two buildings that we lease at Fan Pier in Boston, Massachusetts. We commenced lease payments on these buildings in 2013 and the initial lease periods end in December 2028. We also lease office and laboratory space in San Diego, California. We commenced lease payments for this building in 2019 pursuant to an initial 16 year lease term. We account for each of these buildings as finance leases.

Operating Leases

The remainder of our real estate leases are accounted for as operating leases, including office and laboratory space at our Innovation Square facility near our corporate headquarters. Base rent payments commenced in 2021 pursuant to an initial 15 year lease term for this building.

Our total future minimum lease payments for our finance and operating leases for each of the next five years and in total are included in Note L, “Leases.” The total future undiscounted minimum lease payments were $796.2 million and $482.2 million related to our finance and operating leases, respectively, as of December 31, 2021.

CRITICAL ACCOUNTING POLICIES AND ESTIMATES

Our discussion and analysis of our financial condition and results of operations are based upon our consolidated financial statements prepared in accordance with generally accepted accounting principles in the U.S. The preparation of these financial statements requires us to make certain estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of revenues and expenses during the reported periods. These items are monitored and analyzed by management for changes in facts and circumstances, and material changes in these estimates could occur in the future. Changes in estimates are reflected in reported results for the period in which the change occurs. We base our estimates on historical experience and various other assumptions that we believe to be reasonable under the circumstances. Actual results may differ from our estimates if past experience or other assumptions do not turn out to be substantially accurate.

We believe that our application of the following accounting policies, each of which requires significant judgments and estimates on the part of management, are the most critical to aid in fully understanding and evaluating our reported financial results:

- revenue recognition;
- acquisitions, including intangible assets, goodwill and contingent consideration; and
- income taxes.

Our accounting policies, including the ones discussed below, are more fully described in the Notes to our consolidated financial statements, including Note A, “Nature of Business and Accounting Policies,” included in this Annual Report on Form 10-K.

Revenue Recognition

Product Revenues, Net

We generate product revenues from sales in the U.S. and in international markets. We sell our products principally to a limited number of specialty pharmacy and specialty distributors in the U.S., which account for the largest portion of our total revenues. We make international sales primarily to specialty distributors and retail chains, as well as hospitals and clinics, many of which are government-owned or supported customers. Our customers in the U.S. subsequently resell our products to patients and health care providers. We contract with government agencies so that our products will be eligible for purchase by, or partial or full reimbursement from, such third-party payors. We recognize net product revenues from sales of our products when our customers obtain control of our products, which typically occurs upon delivery to our customers. Revenues from our product sales are recorded at the net sales price, or "transaction price," which requires us to make several significant estimates regarding the net sales price.

The most significant estimate we are required to make is related to government and private payor rebates, chargebacks, discounts and fees, collectively rebates. The value of the rebates provided to third-party payors per course of treatment vary significantly and are based on government-mandated discounts and our arrangements with other third-party payors. In order to estimate our total rebates, we estimate the percentage of prescriptions that will be covered by each third-party payor, which is referred to as the payor mix. We track available information regarding changes, if any, to the payor mix for our products, to our contractual terms with third-party payors and to applicable governmental programs and regulations and levels of our products in the distribution channel. We adjust our estimated rebates based on new information, including information regarding actual rebates for our products, as it becomes available. Claims by third-party payors for rebates are submitted to us significantly after the related sales, potentially resulting in adjustments in the period in which the new information becomes known. Our credits to revenue related to prior period sales, apart from an adjustment to the transaction price for ORKAMBI distributed through early access programs in France in 2019, have not been significant (typically less than 1% of gross product revenues) and primarily related to U.S. rebates.

The following table summarizes activity related to our accruals for rebates (including a refund liability to the French government related to ORKAMBI distributed through early access programs in France, which was paid in 2020) for 2021, 2020 and 2019:

		(in millions)
Balance as of December 31, 2018	$	545.1
Provision related to 2019 sales		656.0
Adjustments related to prior year(s) sales		(95.5)
Credits/payments made		(469.9)
Balance as of December 31, 2019	$	635.7
Provision related to 2020 sales		1,284.1
Adjustments related to prior year(s) sales		0.6
Credits/payments made		(1,144.8)
Balance as of December 31, 2020	$	775.6
Provision related to 2021 sales		2,126.1
Adjustments related to prior year(s) sales		(27.6)
Credits/payments made		(2,035.5)
Balance as of December 31, 2021	$	838.6

We have also entered into annual contracts with government-owned and supported customers in international markets that limit the amount of annual reimbursement we can receive. Upon exceeding the annual reimbursement amount, products are provided free of charge, which is a material right. We defer a portion of the consideration received, which includes upfront payments and fees, for shipments made up to the annual reimbursement limit as "Other current liabilities." The deferred amount is recognized as revenue when the free products are shipped. In order to estimate the portion of the consideration received to recognize as revenue and the portion of the amount to defer, we rely on our forecast of the number of units we will distribute during the applicable annual period in each international market in which our contracts with

government-owned and supported customers limit the amount of annual reimbursement we can receive. Our forecasts are based on, among other things, our historical experience.

The preceding estimates and judgments materially affect our recognition of net product revenues. Changes in our estimates of net product revenues could have a material effect on net product revenues recorded in the period in which we determine that change occurs.

French Early Access Programs

In 2015, we began distributing ORKAMBI through early access programs in France and remained engaged in reimbursement discussions with the French government for ORKAMBI, including ORKAMBI distributed through early access programs, until November 2019, when we reached an agreement with the French government. From the time we began distributing ORKAMBI through early access programs in France, we expected that the difference between the amounts collected based on the invoiced amount and the final amount for ORKAMBI distributed through these programs would be returned to the French government. Our refund liability related to the early access programs in France was classified in "Accrued expenses" on our consolidated balance sheets.

From the first quarter of 2018 through the third quarter of 2019, we recognized net product revenues for ORKAMBI sales in France under the early access programs based on a transaction price that reflected our estimate of consideration we expected to retain that would not be subject to a significant reversal in amounts recognized, which resulted in revenue representing a portion of the invoiced amount.

Upon reaching an agreement with the French government for ORKAMBI, including the final amount for ORKAMBI distributed through early access programs in France in the fourth quarter of 2019, we updated the transaction price related to ORKAMBI distributed through early access programs and recognized net product revenues of $155.8 million related to these shipments, which occurred from 2015 through the date of our agreement with the French government, because the final amount for these shipments exceeded our previous estimate.

Acquisitions

We are required to make several significant judgments and estimates in order to calculate the purchase price for our business combinations and then allocate it to the assets that we have acquired and the liabilities that we have assumed on our consolidated balance sheet. The most significant judgments and estimates relate to the fair value of the in-process research and development assets and contingent consideration liabilities related to these business combinations. Based on these judgments and estimates, the fair value of the goodwill that we record as a result of these business combinations may be material. Once recorded, these assets are subject to quarterly impairment analysis and our contingent consideration liability is adjusted quarterly, which requires similar judgments and estimates.

Intangible Assets

In 2019, we recorded in-process research and development assets related to our acquisitions of Exonics and Semma totaling $400.0 million on our consolidated balance sheet, which remained on our consolidated balance sheet as of December 31, 2021. Each of these assets is accounted for as an indefinite-lived intangible asset and is maintained on our consolidated balance sheet until either the project underlying it is completed or the asset becomes impaired. When we determine that an asset has become impaired or we abandon a project, we write down the carrying value of the related intangible asset to its fair value and record an impairment charge in the period in which the impairment occurs.

To determine the fair value of our in-process research and development assets, we utilize the multi-period excess earnings method of the income approach, which requires us to make estimates of the probability of technical and regulatory success, development cost assumptions, revenue projections and growth rates, commercial cost estimates and appropriate discount rates. These assumptions require significant management judgment and reasonable changes in the assumptions can cause material changes to the fair value of the intangible assets. Due to the early stage of Exonics and Semma's programs, these significant assumptions could be affected by future economic and market conditions.

Contingent Consideration

As of December 31, 2021 and 2020, we had $186.5 million and $189.6 million, respectively, of liabilities on our consolidated balance sheet attributable to the fair value of the contingent development and regulatory payments that we may

owe to Exonics' former equity holders upon the achievement of certain events.

We record an increase or a decrease in the fair value of the contingent consideration liability on our consolidated balance sheet and in our consolidated statement of operations on a quarterly basis. We determine the fair value of our contingent consideration liability using a probability weighted discounted cash flow method of the income approach, which requires us to make estimates of the timing of regulatory and commercial milestone achievement and the corresponding estimated probability of technical and regulatory success rates. Significant judgment is used in determining the appropriateness of these assumptions during each reporting period. Reasonable changes in these assumptions can cause material changes to the fair value of our contingent consideration liability. Due to the early stage of Exonics' DMD and DM1 programs, these significant assumptions could be affected by future economic and market conditions.

Goodwill

In 2021 and 2020, we did not have any business combinations; therefore, we did not record any additional goodwill on our consolidated balance sheet. In 2019, we recorded goodwill of $554.6 million and $397.1 million related to our acquisitions of Semma and Exonics, respectively. Goodwill reflects the difference between the fair value of the consideration transferred and the fair value of the net assets acquired. Thus, the goodwill that we record is dependent on the significant judgments and estimates inherent in the fair value of our in-process research and development assets and contingent consideration liabilities. We have one reporting unit for goodwill reporting purposes. We have not identified any goodwill impairment to date.

Income Taxes

We utilize the asset and liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are determined based on the difference between the financial statement carrying amounts and tax basis of assets and liabilities using enacted tax rates in effect for years in which the temporary differences are expected to reverse. If our estimate of the tax effect of reversing temporary differences is (i) not reflective of actual outcomes, (ii) modified to reflect new developments or interpretations of the tax law, or (iii) revised to incorporate new accounting principles, or changes in the expected timing or manner of the reversal, our results of operations could be materially impacted.

We provide a valuation allowance when it is more likely than not that deferred tax assets will not be realized. On a periodic basis, we reassess our valuation allowances on our deferred tax assets, weighing positive and negative evidence to assess the recoverability of the deferred tax assets. Significant judgment is required in making these assessments to maintain or reverse our valuation allowances and, to the extent our future expectations change we would have to assess the recoverability of these deferred tax assets at that time. As of December 31, 2021, we maintained a valuation allowance of $220.4 million related primarily to U.S. state and foreign tax attributes.

We record liabilities related to uncertain tax positions by prescribing a minimum recognition threshold and measurement attribute for the financial statement recognition and measurement of a tax position taken or expected to be taken in a tax return. We adjust our liability to reflect any subsequent changes in the relevant facts and circumstances surrounding the uncertain positions. Significant judgment is required in making this assessment, and, therefore, we re-evaluate uncertain tax positions and consider various factors, including, but not limited to, changes in tax law, the measurement of tax positions taken or expected to be taken in tax returns, and changes in facts or circumstances related to a tax position.

RECENT ACCOUNTING PRONOUNCEMENTS

Refer to Note A, "Nature of Business and Accounting Policies," in the accompanying notes to the consolidated financial statements for a discussion of recent accounting pronouncements and new accounting pronouncements adopted during 2021.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

As part of our investment portfolio, we own financial instruments that are sensitive to market risks. The investment portfolio is used to preserve our capital. None of these market risk-sensitive instruments are held for trading purposes. We do not have derivative financial instruments in our investment portfolio.

Interest Rate Risk

We invest our cash in a variety of financial instruments, principally securities issued by the U.S. government and its agencies, investment-grade corporate bonds and commercial paper, and money market funds. These investments are denominated in U.S. Dollars. All of our interest-bearing securities are subject to interest rate risk and could decline in value if interest rates fluctuate, including potential fluctuations as a result of COVID-19. Substantially all of our investment portfolio consists of marketable securities with active secondary or resale markets to help ensure portfolio liquidity, and we have implemented guidelines limiting the term-to-maturity of our investment instruments. Due to the conservative nature of these instruments, we do not believe that we have material exposure to interest rate risk. If interest rates were to increase or decrease by 1%, the fair value of our investment portfolio would increase or decrease by an immaterial amount.

We entered into a credit agreement in each of 2020 and 2019. Loans under these credit agreements bear interest, at our option, at either a base rate or a Eurocurrency rate, in each case plus an applicable margin based on our consolidated leverage ratio (the ratio of our total consolidated funded indebtedness to our consolidated EBITDA for the most recently completed four fiscal quarter period). Pursuant to the credit agreement that we entered into in 2019, the applicable margin on base rate loans ranges from 0.125% to 0.500% and the applicable margin on Eurocurrency loans ranges from 1.125% to 1.500%. Pursuant to the credit agreement that we entered into in 2020, the applicable margin on base rate loans ranges from 0.500% to 0.875% and the applicable margin on Eurocurrency loans ranges from 1.500% to 1.875%. We do not believe that changes in interest rates related to either credit agreement would have a material effect on our consolidated financial statements. As of December 31, 2021, we had no principal or interest outstanding under either of our existing credit facilities. A portion of our “Interest expense” in 2022 will be dependent on whether, and to what extent, we borrow amounts under these existing facilities.

Foreign Exchange Market Risk

As a result of our foreign operations, we face exposure to movements in foreign currency exchange rates, primarily the Euro and British Pound against the U.S. Dollar. Fluctuations in the global markets, including as a result of COVID-19, may have a positive or negative effect on our foreign exchange rate exposure. The current exposures arise primarily from cash, accounts receivable, intercompany receivables and payables, payables and accruals and inventories. Both positive and negative effects to our net revenues from international product sales from movements in exchange rates are partially mitigated by the natural, opposite effect that exchange rates have on our international operating costs and expenses.

We have a foreign currency management program with the objective of reducing the effect of exchange rate fluctuations on our operating results and forecasted revenues and expenses denominated in foreign currencies. We currently have cash flow hedges for the Euro, British Pound, Canadian Dollar, Swiss Franc and Australian Dollar related to a portion of our forecasted product revenues that qualify for hedge accounting treatment under U.S. GAAP. We do not seek hedge accounting treatment for our foreign currency forward contracts related to monetary assets and liabilities that impact our operating results. As of December 31, 2021, we held foreign exchange forward contracts that were designated as cash flow hedges with notional amounts totaling $1.9 billion representing a net fair value of $38.2 million recorded on our consolidated balance sheet.

Although not predictive in nature, we believe a hypothetical 10% threshold reflects a reasonably possible near-term change in exchange rates. If the December 31, 2021 exchange rates were to change by a hypothetical 10%, the fair value recorded on our consolidated balance sheet related to our foreign exchange forward contracts that were designated as cash flow hedges as of December 31, 2021 would change by approximately $189.3 million. However, since these contracts hedge a specific portion of our forecasted product revenues denominated in certain foreign currencies, any change in the fair value of these contracts is recorded in “Accumulated other comprehensive income (loss)” on our consolidated balance sheet and is reclassified to earnings in the same periods during which the underlying product revenues affect earnings. Therefore, any change in the fair value of these contracts that would result from a hypothetical 10% change in exchange rates would be entirely offset by the change in value associated with the underlying hedged product revenues resulting in no impact on our future anticipated earnings and cash flows with respect to the hedged portion of our forecasted product revenues.

Equity Price Risk

Information required by this section is incorporated by reference from the discussion in the "Strategic Investments" section of this Part II, Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations."

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

The information required by this Item 8 is contained on pages F-1 through F-45 of this Annual Report on Form 10-K.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

Not applicable.

ITEM 9A. CONTROLS AND PROCEDURES

(1) 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) and Rule 15d-15(e) promulgated under the Securities Exchange Act of 1934, as amended) as of the end of the period covered by this Annual Report on Form 10-K, have concluded that, based on such evaluation, our disclosure controls and procedures were effective. In designing and evaluating the disclosure controls and procedures, management recognized that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives, and management necessarily was required to apply our judgment in evaluating the cost-benefit relationship of possible controls and procedures.

(2) Management's Annual Report on Internal Control Over Financial Reporting. Management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rule 13a-15(f) and Rule 15d-15(f) promulgated under the Securities Exchange Act of 1934, as amended, as a process designed by, or under the supervision of, our principal executive and principal financial officers and effected by our board of directors, management and other personnel, 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. Our internal control over financial reporting include those policies and procedures that:

- pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of our assets;
- provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that our receipts and expenditures are being made only in accordance with authorizations of management and our directors; and
- provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our 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.

Management assessed the effectiveness of our internal control over financial reporting as of December 31, 2021. In making this assessment, we used the criteria set forth in the *Internal Control—Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). Based on our assessment, management has concluded that, as of December 31, 2021, our internal control over financial reporting is effective based on those criteria.

Our independent registered public accounting firm, Ernst & Young LLP, issued an attestation report on our internal control over financial reporting. See Section 4 below.

(3) Changes in Internal Controls. During the quarter ended December 31, 2021, there were no changes in our internal control over financial reporting that materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

(4) Report of Independent Registered Public Accounting Firm

To the Shareholders and the Board of Directors of Vertex Pharmaceuticals Incorporated

Opinion on Internal Control over Financial Reporting

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

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the 2021 consolidated financial statements of the Company and our report dated February 9, 2022, expressed an unqualified opinion thereon.

Basis for Opinion

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

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control over Financial Reporting

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

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

/s/ Ernst & Young LLP

Boston, Massachusetts
February 9, 2022

ITEM 9B. OTHER INFORMATION

On February 7, 2022, the Company entered into an amendment to Dr. Jeffrey Leiden's employment agreement, which was scheduled to expire on March 31, 2023. Among other things, the amendment extends the term for one year through March 31, 2024 and provides that Dr. Leiden's equity compensation during the final year of the amended employment agreement will be equivalent to his equity compensation in the preceding year. The foregoing description of the amendment to Dr. Leiden's employment agreement does not purport to be complete and is qualified in its entirety by reference to the full text of such agreement, which is filed as Exhibit 10.24 to this Annual Report on Form 10-K and incorporated by reference herein.

PART III

Portions of our definitive Proxy Statement for the 2022 Annual Meeting of Shareholders, or 2022 Proxy Statement, are incorporated by reference into this Part III of our Annual Report on Form 10-K.

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information regarding directors required by this Item 10 will be included in our 2022 Proxy Statement and is incorporated herein by reference. We expect this information to be provided under “Election of Directors,” “Corporate Governance and Risk Management,” “Shareholder Proposals for the 2022 Annual Meeting and Nominations for Director,” “Delinquent Section 16(a) Reports” and “Code of Conduct.” The information regarding executive officers required by this Item 10 is included in Part I of this Annual Report on Form 10-K.

ITEM 11. EXECUTIVE COMPENSATION

The information required by this Item 11 will be included in the 2022 Proxy Statement and is incorporated herein by reference. We expect this information to be provided under “Compensation Committee Interlocks and Insider Participation,” “Compensation Discussion and Analysis,” “Compensation and Equity Tables,” “Director Compensation,” “Management Development and Compensation Committee Report” and/or “Corporate Governance and Risk Management.”

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required by this Item 12 will be included in the 2022 Proxy Statement and is incorporated herein by reference. We expect this information to be provided under “Security Ownership of Certain Beneficial Owners and Management” and “Equity Compensation Plan Information.”

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The information required by this Item 13 will be included in the 2022 Proxy Statement and is incorporated herein by reference. We expect this information to be provided under “Election of Directors,” “Corporate Governance and Risk Management,” and “Audit and Finance Committee.”

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES

The information required by this Item 14 will be included in the 2022 Proxy Statement and is incorporated herein by reference. We expect this information to be provided under “Ratification of the Appointment of Independent Registered Public Accounting Firm.”

PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

(a)(1) The Financial Statements required to be filed by Items 8 and 15(c) of Form 10-K, and filed herewith, are as follows:

(a)(2) Financial Statement Schedules have been omitted because they are either not applicable or the required information is included in the consolidated financial statements or notes thereto listed in (a)(1) above.

(a)(3) Exhibits.

The following is a list of exhibits filed as part of this Annual Report on Form 10-K.

Exhibit Number	Exhibit Description	Filed with this report	Incorporated by Reference herein from —Form or Schedule	Filing Date/ Period Covered	SEC File/Reg. Number
Plan of Acquisition					
2.1	Agreement and Plan of Merger, dated as of June 6, 2019, among Vertex Pharmaceuticals Incorporated, VXP Merger Sub, Inc., Exonics Therapeutics, Inc. and Shareholder Representative Services LLC, solely in its Capacity as Shareholders' Representative, as amended by the Amendment to Agreement and Plan of Merger, dated as of June 12, 2019, among Vertex Pharmaceuticals Incorporated, VXP Merger Sub, Inc., Exonics Therapeutics, Inc. and Shareholder Representative Services LLC, solely in its Capacity as Shareholders' Representative.†		10-Q (Exhibit 10.1)	August 1, 2019	000-19319
Governance Documents					
3.1	Restated Articles of Organization of Vertex Pharmaceuticals Incorporated, as amended.		10-Q (Exhibit 3.1)	July 26, 2018	000-19319
3.2	Amended and Restated By-Laws of Vertex Pharmaceuticals Incorporated.		10-Q (Exhibit 3.2)	May 1, 2020	000-19319
Stock Certificate					
4.1	Specimen Stock Certificate.		10-K (Exhibit 4.1)	February 15, 2018	000-19319
4.2	Description of Securities.		10-K (Exhibit 4.2)	February 13, 2020	000-19319
Collaboration Agreement					
10.1	Research, Development and Commercialization Agreement, dated as of May 24, 2004, between Vertex Pharmaceuticals Incorporated and Cystic Fibrosis Foundation Therapeutics Incorporated.†		10-Q (Exhibit 10.1)	November 3, 2021	000-19319
10.2	Amendment No. 1 to Research, Development and Commercialization Agreement, dated as of January 6, 2006, between Vertex Pharmaceuticals Incorporated and Cystic Fibrosis Foundation Therapeutics Incorporated.†		10-Q (Exhibit 10.2)	November 3, 2021	000-19319
10.3	Amendment No. 2 to Research, Development and Commercialization Agreement, dated as of March 17, 2006, between Vertex Pharmaceuticals Incorporated and Cystic Fibrosis Foundation Therapeutics Incorporated.		10-Q/A (Exhibit 10.6)	August 19, 2011	000-19319
10.4	Amendment No. 5 to Research, Development and Commercialization Agreement, effective as of April 1, 2011, between Vertex Pharmaceuticals Incorporated and Cystic Fibrosis Foundation Therapeutics Incorporated.†		10-Q (Exhibit 10.3)	November 3, 2021	000-19319

Exhibit Number	Exhibit Description	Filed with this report	Incorporated by Reference herein from —Form or Schedule	Filing Date/ Period Covered	SEC File/Reg. Number
10.5	Amendment No. 7 to Research, Development and Commercialization Agreement, dated October 13, 2016, between Vertex Pharmaceuticals Incorporated and Cystic Fibrosis Foundation Therapeutics Incorporated.†		10-Q (Exhibit 10.4)	November 3, 2021	000-19319
10.6	Amended and Restated Joint Development and Commercialization Agreement, dated April 16, 2021, between Vertex Pharmaceuticals Incorporated, Vertex Pharmaceuticals (Europe) Limited and CRISPR Therapeutics AG, CRISPR Therapeutics Limited, CRISPR Therapeutics, Inc., TRACR Hematology Ltd.†		10-Q (Exhibit 10.1)	July 30, 2021	000-19319
Leases					
10.7	Lease, dated May 5, 2011, between Fifty Northern Avenue LLC and Vertex Pharmaceuticals Incorporated.†		10-Q (Exhibit 10.2)	July 30, 2021	000-19319
10.8	Lease, dated May 5, 2011, between Eleven Fan Pier Boulevard LLC and Vertex Pharmaceuticals Incorporated.†		10-Q (Exhibit 10.3)	July 30, 2021	000-19319
Financing Agreements					
10.9	Credit Agreement, dated as of September 17, 2019, by and among Vertex Pharmaceuticals Incorporated, Bank of America, N.A. and the other lenders party thereto.		10-Q (Exhibit 10.1)	October 31, 2019	000-19319
10.10	First Amendment to Credit Agreement, dated as of December 29, 2020, by and among Vertex Pharmaceuticals Incorporated, Bank of America, N.A. and the other lender parties thereto.		10-K (Exhibit 10.10)	February 11, 2021	000-19319
10.11	Credit Agreement, dated as of September 18, 2020, by and among Vertex Pharmaceuticals Incorporated, Bank of America, N.A. and the other lender parties thereto.		10-Q (Exhibit 10.1)	October 30, 2020	000-19319
Equity Plans					
10.12	Amended and Restated 2006 Stock and Option Plan.*		10-Q (Exhibit 10.1)	October 25, 2018	000-19319
10.13	Form of Stock Option Agreement under Amended and Restated 2006 Stock and Option Plan (granted prior to July 30, 2013).*		8-K (Exhibit 10.2)	May 15, 2006	000-19319
10.14	Form of Stock Option Agreement under Amended and Restated 2006 Stock and Option Plan (granted on or after July 30, 2013).*		10-K (Exhibit 10.20)	February 13, 2015	000-19319
10.15	Amended and Restated 2013 Stock and Option Plan.*		DEF 14A (Appendix A)	April 26, 2019	000-19319
10.16	Form of Non-Qualified Stock Option Agreement under 2013 Stock and Option Plan.*		10-K (Exhibit 10.17)	February 13, 2015	000-19319
10.17	Form of Restricted Stock Agreement under 2013 Stock and Option Plan.*		10-K (Exhibit 10.18)	February 13, 2015	000-19319
10.18	Form of Restricted Stock Unit Agreement under 2013 Stock and Option Plan (U.S.).*		10-K (Exhibit 10.25)	February 16, 2016	000-19319
10.19	Form of Restricted Stock Unit Agreement under 2013 Stock and Option Plan (International).*		10-K (Exhibit 10.19)	February 13, 2015	000-19319
10.20	Form of Restricted Stock Unit Agreement Under 2013 Stock and Option Plan.*		10-K (Exhibit 10.17)	February 13, 2020	000-19319
10.21	Non-Employee Director Deferred Compensation Plan.*		10-K (Exhibit 10.27)	February 16, 2016	000-19319
10.22	Vertex Pharmaceuticals Incorporated Employee Stock Purchase Plan.*		DEF 14A (Appendix B)	April 26, 2019	000-19319
Agreements with Executive Officers and Directors					
10.23	Employment Agreement, dated as of April 1, 2020, by and between Vertex Pharmaceuticals Incorporated and Jeffrey M. Leiden, M.D., Ph.D.*		8-K (Exhibit 10.1)	April 1, 2020	000-19319
10.24	Amendment No. 1 to Employment Agreement, between Jeffrey M. Leiden and Vertex Pharmaceuticals Incorporated, dated as of February 7, 2022.*	X			
10.25	Employee Non-disclosure, Non-competition and Inventions Agreement between Jeffrey M. Leiden and Vertex Pharmaceuticals Incorporated, dated December 14, 2011.*		10-K (Exhibit 10.35)	February 22, 2012	000-19319
10.26	Employment Agreement, dated as of July 24, 2019, between Vertex Pharmaceuticals Incorporated and Reshma Kewalramani.*		8-K (Exhibit 10.1)	July 25, 2019	000-19319
10.27	Change of Control Agreement, dated as of July 24, 2019, between Vertex Pharmaceuticals Incorporated and Reshma Kewalramani.*		8-K (Exhibit 10.2)	July 25, 2019	000-19319
10.28	Employment Agreement, dated as of August 27, 2012, between Vertex Pharmaceuticals Incorporated and Stuart Arbuckle.*		10-Q (Exhibit 10.1)	November 6, 2012	000-19319

Exhibit Number	Exhibit Description	Filed with this report	Incorporated by Reference herein from —Form or Schedule	Filing Date/ Period Covered	SEC File/Reg. Number
10.29	Change of Control Agreement, dated as of August 27, 2012, between Vertex Pharmaceuticals Incorporated and Stuart Arbuckle.*		10-Q (Exhibit 10.2)	November 6, 2012	000-19319
10.30	Employment Agreement, dated as of December 12, 2014, between Vertex Pharmaceuticals Incorporated and David Altshuler.*		10-K (Exhibit 10.34)	February 16, 2016	000-19319
10.31	Change of Control Agreement, dated as of December 10, 2014, between Vertex Pharmaceuticals Incorporated and David Altshuler.*		10-K (Exhibit 10.35)	February 16, 2016	000-19319
10.32	Third Amended and Restated Employment Agreement, dated as of February 26, 2013, between Vertex Pharmaceuticals Incorporated and Amit Sachdev.*		10-K (Exhibit 10.42)	February 23, 2017	000-19319
10.33	Third Amended and Restated Change of Control Agreement, dated as of February 26, 2013, between Vertex Pharmaceuticals Incorporated and Amit Sachdev.*		10-K (Exhibit 10.43)	February 23, 2017	000-19319
10.34	Employment Agreement, dated March 28, 2019, by and between Vertex Pharmaceuticals Incorporated and Charles F. Wagner, Jr.*		10-Q (Exhibit 10.1)	May 1, 2019	000-19319
10.35	Change of Control Agreement, dated as of March 28, 2019, by and between Vertex Pharmaceuticals Incorporated and Charles F. Wagner, Jr.*		10-Q (Exhibit 10.2)	May 1, 2019	000-19319
10.36	Employment Agreement, dated August 1, 2020, by and between Vertex Pharmaceuticals Incorporated and Nia Tatsis.*	X			
10.37	Change of Control Agreement, dated August 1, 2020, by and between Vertex Pharmaceuticals Incorporated and Nia Tatsis.*	X			
10.38	Vertex Pharmaceuticals Employee Compensation Plan.*		10-K (Exhibit 10.46)	February 15, 2018	000-19319
10.39	Vertex Pharmaceuticals Non-Employee Board Compensation.*	X			
Subsidiaries					
21.1	Subsidiaries of Vertex Pharmaceuticals Incorporated.	X			
Consent					
23.1	Consent of Independent Registered Public Accounting Firm, Ernst & Young LLP.	X			
Certifications					
31.1	Certification of the Chief Executive Officer under Section 302 of the Sarbanes-Oxley Act of 2002.	X			
31.2	Certification of the Chief Financial Officer under Section 302 of the Sarbanes-Oxley Act of 2002.	X			
32.1	Certification of the Chief Executive Officer and the Chief Financial Officer under Section 906 of the Sarbanes-Oxley Act of 2002.	X			
101.INS	XBRL Instance	X			
101.SCH	XBRL Taxonomy Extension Schema	X			
101.CAL	XBRL Taxonomy Extension Calculation	X			
101.LAB	XBRL Taxonomy Extension Labels	X			
101.PRE	XBRL Taxonomy Extension Presentation	X			
101.DEF	XBRL Taxonomy Extension Definition	X			
104	Cover Page Interactive Data File—the cover page interactive data file does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document.	X			

* Management contract, compensatory plan or agreement.

† Confidential portions of this document have been redacted according to the applicable rules.

ITEM 16. FORM 10-K SUMMARY

Not applicable.

SIGNATURES

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

Vertex Pharmaceuticals Incorporated

February 9, 2022 By: /s/ Reshma Kewalramani

Reshma Kewalramani
Chief Executive Officer

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.

Name	Title	Date
/s/ Reshma Kewalramani Reshma Kewalramani	President, Chief Executive Officer and Director (Principal Executive Officer)	February 9, 2022
/s/ Charles F. Wagner, Jr. Charles F. Wagner, Jr.	Executive Vice President and Chief Financial Officer (Principal Financial Officer)	February 9, 2022
/s/ Kristen C. Ambrose Kristen C. Ambrose	Senior Vice President and Chief Accounting Officer (Principal Accounting Officer)	February 9, 2022
/s/Jeffrey M. Leiden Jeffrey M. Leiden	Executive Chairman	February 9, 2022
/s/ Sangeeta N. Bhatia Sangeeta N. Bhatia	Director	February 9, 2022
/s/ Lloyd Carney Lloyd Carney	Director	February 9, 2022
/s/ Alan Garber Alan Garber	Director	February 9, 2022
/s/ Terrence C. Kearney Terrence C. Kearney	Director	February 9, 2022
/s/ Yuchun Lee Yuchun Lee	Director	February 9, 2022
/s/ Margaret G. McGlynn Margaret G. McGlynn	Director	February 9, 2022
/s/ Diana McKenzie Diana McKenzie	Director	February 9, 2022
/s/ Bruce I. Sachs Bruce I. Sachs	Director	February 9, 2022

Report of Independent Registered Public Accounting Firm

To the Shareholders and the Board of Directors of Vertex Pharmaceuticals Incorporated

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Vertex Pharmaceuticals Incorporated (the Company) as of December 31, 2021 and 2020, the related consolidated statements of operations, comprehensive income, shareholders' equity, and cash flows for each of the three years in the period ended December 31, 2021, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at 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 U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2021, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 9, 2022, expressed an unqualified opinion thereon.

Basis for Opinion

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

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the 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 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 financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

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

Revenue recognition - Payor Mix Impact on Measuring Variable Consideration

Description of the Matter

As discussed in Note A to the Company's consolidated financial statements, the Company records product sales at the net sales price, or "transaction price," which requires the Company to make several significant estimates regarding the net sales price. The most significant estimates relate to government rebates, chargebacks, discounts and fees, collectively rebates. Due to the delay in receipt of claims by third-party payors, the Company estimates the percentage of prescriptions that will be covered by each third-party payor, which is referred to as the payor mix. Rebate accruals inclusive of estimated amounts due for claims not yet received or processed are recorded within accrued expenses on the Company's consolidated balance sheet.

Auditing the measurement of the Company's net product revenues was complex and judgmental due to the significant estimation required in determining the amount of consideration that will be collected net of estimates for payor rebates. In particular, the net sales price is affected by assumptions in payor behavior such as changes in payor mix, payor collections, current customer contractual requirements, and experience with ultimate collection from third-party payors.

How We Addressed the Matter in Our Audit

We obtained an understanding, evaluated the design and tested the operating effectiveness of controls over the Company's revenue recognition process, including controls over the underlying assumptions and inputs used by management to estimate amounts due to third-party payors and the completeness and accuracy of the data used in the estimates. We also tested the Company's controls to assess the completeness and accuracy of the current and historical data that supports the estimate.

Our audit procedures to test the Company's recognition of net product revenues included, among others, assessing the methodology used to determine the estimate and testing the significant assumptions and the underlying data used by the Company in its analysis, which included historical claims data. To assess the payor mix assumptions we tested contracted rates, historical claims and payment data and related trends, and other relevant factors. We also assessed the historical accuracy of the Company's estimates of third-party payor rebates.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2005.

Boston, Massachusetts
February 9, 2022

VERTEX PHARMACEUTICALS INCORPORATED

Consolidated Statements of Operations

(in millions, except per share amounts)

	Year Ended December 31,		
	2021	**2020**	**2019**
Revenues:			
Product revenues, net	$ 7,573.4	$ 6,202.8	$ 4,160.7
Other revenues	1.0	2.9	2.1
Total revenues	7,574.4	6,205.7	4,162.8
Costs and expenses:			
Cost of sales	904.2	736.3	547.8
Research and development expenses	3,051.1	1,829.5	1,754.5
Selling, general and administrative expenses	840.1	770.5	658.5
Change in fair value of contingent consideration	(3.1)	13.1	4.5
Total costs and expenses	4,792.3	3,349.4	2,965.3
Income from operations	2,782.1	2,856.3	1,197.5
Interest income	4.9	22.2	63.7
Interest expense	(61.5)	(58.2)	(58.5)
Other income, net	4.9	296.6	192.2
Income before provision for income taxes	2,730.4	3,116.9	1,394.9
Provision for income taxes	388.3	405.2	218.1
Net income	$ 2,342.1	$ 2,711.7	$ 1,176.8
Net income per common share:			
Basic	$ 9.09	$ 10.44	$ 4.58
Diluted	$ 9.01	$ 10.29	$ 4.51
Shares used in per share calculations:			
Basic	257.7	259.8	256.7
Diluted	259.9	263.4	260.7

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

VERTEX PHARMACEUTICALS INCORPORATED

Consolidated Statements of Comprehensive Income

(in millions)

	Year ended December 31,		
	2021	**2020**	**2019**
Net income	$ 2,342.1	$ 2,711.7	$ 1,176.8
Other comprehensive income:			
Unrealized holding (losses) gains on marketable securities, net	(0.8)	(0.2)	1.0
Unrealized gains (losses) on foreign currency forward contracts, net of tax of $(21.8), $14.3 and $7.0, respectively	83.2	(51.6)	(14.0)
Foreign currency translation adjustment	2.0	(14.7)	10.3
Total other comprehensive income (loss)	84.4	(66.5)	(2.7)
Comprehensive income	$ 2,426.5	$ 2,645.2	$ 1,174.1

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

VERTEX PHARMACEUTICALS INCORPORATED

Consolidated Balance Sheets

(in millions, except share data)

	December 31,	
	2021	**2020**
Assets		
Current assets:		
Cash and cash equivalents	$ 6,795.0	$ 5,988.2
Marketable securities	729.9	670.7
Accounts receivable, net	1,136.8	885.4
Inventories	353.1	280.8
Prepaid expenses and other current assets	545.8	308.3
Total current assets	9,560.6	8,133.4
Property and equipment, net	1,094.1	958.5
Goodwill	1,002.2	1,002.2
Intangible assets	400.0	400.0
Deferred tax assets	934.5	882.8
Operating lease assets	330.3	325.6
Other assets	110.8	49.3
Total assets	$ 13,432.5	$ 11,751.8
Liabilities and Shareholders' Equity		
Current liabilities:		
Accounts payable	$ 195.0	$ 155.1
Accrued expenses	1,678.6	1,405.0
Other current liabilities	268.4	317.4
Total current liabilities	2,142.0	1,877.5
Long-term finance lease liabilities	509.8	539.0
Long-term operating lease liabilities	377.4	350.5
Long-term contingent consideration	186.5	189.6
Other long-term liabilities	116.8	108.4
Total liabilities	3,332.5	3,065.0
Commitments and contingencies	—	—
Shareholders' equity:		
Preferred stock, $0.01 par value; 1,000,000 shares authorized; none issued and outstanding	—	—
Common stock, $0.01 par value; 500,000,000 shares authorized, 254,479,046 and 259,889,549 shares issued and outstanding, respectively	2.5	2.6
Additional paid-in capital	6,880.8	7,894.0
Accumulated other comprehensive income (loss)	15.9	(68.5)
Retained earnings	3,200.8	858.7
Total shareholders' equity	10,100.0	8,686.8
Total liabilities and shareholders' equity	$ 13,432.5	$ 11,751.8

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

VERTEX PHARMACEUTICALS INCORPORATED

Consolidated Statements of Shareholders' Equity

(in millions)

	Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Income (Loss)	Retained Earnings (Accumulated Deficit)	Total Shareholders' Equity
	Shares	Amount				
Balance, December 31, 2018	255.2	$ 2.5	$ 7,421.5	$ 0.7	$ (2,989.5)	$ 4,435.2
Cumulative effect adjustment for adoption of new accounting guidance	—	—	—	—	(40.3)	(40.3)
Other comprehensive loss, net of tax	—	—	—	(2.7)	—	(2.7)
Net income	—	—	—	—	1,176.8	1,176.8
Repurchases of common stock	(1.0)	0.0	(186.0)	—	—	(186.0)
Common stock withheld for employee tax obligations	—	—	(6.0)	—	—	(6.0)
Issuance of common stock under benefit plans	4.8	0.1	345.9	—	—	346.0
Stock-based compensation expense	—	—	362.2	—	—	362.2
Balance, December 31, 2019	259.0	$ 2.6	$ 7,937.6	$ (2.0)	$ (1,853.0)	$ 6,085.2
Other comprehensive loss, net of tax	—	—	—	(66.5)	—	(66.5)
Net income	—	—	—	—	2,711.7	2,711.7
Repurchases of common stock	(2.4)	0.0	(539.1)	—	—	(539.1)
Common stock withheld for employee tax obligations	(0.8)	0.0	(200.3)	—	—	(200.3)
Issuance of common stock under benefit plans	4.1	0.0	262.7	—	—	262.7
Stock-based compensation expense	—	—	433.1	—	—	433.1
Balance, December 31, 2020	259.9	$ 2.6	$ 7,894.0	$ (68.5)	$ 858.7	$ 8,686.8
Other comprehensive income, net of tax	—	—	—	84.4	—	84.4
Net income	—	—	—	—	2,342.1	2,342.1
Repurchases of common stock	(7.3)	(0.1)	(1,425.3)	—	—	(1,425.4)
Common stock withheld for employee tax obligations	(0.6)	0.0	(135.9)	—	—	(135.9)
Issuance of common stock under benefit plans	2.5	0.0	102.5	—	—	102.5
Stock-based compensation expense	—	—	445.5	—	—	445.5
Balance, December 31, 2021	254.5	$ 2.5	$ 6,880.8	$ 15.9	$ 3,200.8	$ 10,100.0

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

VERTEX PHARMACEUTICALS INCORPORATED

Consolidated Statements of Cash Flows

(in millions)

	Year Ended December 31,		
	2021	**2020**	**2019**
Cash flows from operating activities:			
Net income	$ 2,342.1	$ 2,711.7	$ 1,176.8
Adjustments to reconcile net income to net cash provided by operating activities:			
Stock-based compensation expense	441.4	429.5	360.5
Depreciation expense	125.6	109.5	106.9
Deferred income taxes	(154.6)	277.3	167.4
Gains on equity securities	(17.1)	(311.9)	(197.6)
(Decrease) increase in fair value of contingent consideration	(3.1)	13.1	4.5
Other non-cash items, net	14.4	78.7	16.9
Changes in operating assets and liabilities:			
Accounts receivable, net	(274.7)	(223.4)	(225.6)
Inventories	(92.8)	(132.0)	(64.0)
Prepaid expenses and other assets	(91.8)	(297.6)	35.4
Accounts payable	31.9	51.3	(22.8)
Accrued expenses	305.4	122.2	172.9
Other liabilities	16.8	425.1	38.0
Net cash provided by operating activities	2,643.5	3,253.5	1,569.3
Cash flows from investing activities:			
Payments to acquire businesses, net of cash acquired	—	—	(1,154.2)
Purchases of available-for-sale debt securities	(528.2)	(431.4)	(537.2)
Maturities of available-for-sale debt securities	499.3	372.3	475.9
Sale of equity securities	—	437.6	94.9
Purchases of property and equipment	(235.0)	(259.8)	(75.4)
Investment in equity securities and notes receivable	(77.0)	(19.3)	(39.3)
Net cash (used in) provided by investing activities	(340.9)	99.4	(1,235.3)
Cash flows from financing activities:			
Issuances of common stock under benefit plans	102.0	264.9	343.2
Repurchases of common stock	(1,425.4)	(539.1)	(186.0)
Payments in connection with common stock withheld for employee tax obligations	(135.9)	(200.3)	(6.0)
Payments on finance leases	(47.0)	(42.3)	(39.2)
Proceeds from finance leases	22.6	13.3	10.0
Other financing activities	5.7	(1.8)	4.8
Net cash (used in) provided by financing activities	(1,478.0)	(505.3)	126.8
Effect of changes in exchange rates on cash	(13.4)	20.6	1.6
Net increase in cash, cash equivalents and restricted cash	811.2	2,868.2	462.4
Cash, cash equivalents and restricted cash—beginning of period	5,988.9	3,120.7	2,658.3
Cash, cash equivalents and restricted cash—end of period	$ 6,800.1	$ 5,988.9	$ 3,120.7
Supplemental disclosure of cash flow information:			
Cash paid for interest	$ 56.3	$ 54.5	$ 55.6
Cash paid for income taxes	$ 476.3	$ 191.8	$ 24.7

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

A. Nature of Business and Accounting Policies

Business

Vertex Pharmaceuticals Incorporated ("Vertex," "we," "us" or "our") is global biotechnology company that invests in scientific innovation to create transformative medicines for people with serious diseases with a focus on specialty markets. We have multiple approved medicines that treat the underlying cause of cystic fibrosis ("CF"), a life-threatening genetic disease, and we have several ongoing clinical and research programs to advance and extend treatment of CF. Beyond CF, we have a pipeline of investigational therapies in other serious diseases where we are leveraging insight into causal human biology, including sickle cell disease, beta thalassemia, APOL1-mediated kidney disease, type 1 diabetes, pain, alpha-1 antitrypsin deficiency, and muscular dystrophies.

Our marketed CF medicines are TRIKAFTA/KAFTRIO (elexacaftor/tezacaftor/ivacaftor and ivacaftor), SYMDEKO/SYMKEVI (tezacaftor in combination with ivacaftor), ORKAMBI (lumacaftor in combination with ivacaftor) and KALYDECO (ivacaftor).

Basis of Presentation

The accompanying consolidated financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States of America ("U.S. GAAP"), reflect the operations of Vertex and our wholly-owned subsidiaries. All material intercompany balances and transactions have been eliminated. We operate in one segment, pharmaceuticals. Please refer to Note Q, "Segment Information," for enterprise-wide disclosures regarding our revenues, major customers and long-lived assets by geographic area.

Use of Estimates

The preparation of consolidated financial statements in accordance with U.S. GAAP requires us to make certain estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of our consolidated financial statements, and the amounts of revenues and expenses during the reported periods. We base our estimates on historical experience and various other assumptions, including in certain circumstances future projections that we believe to be reasonable under the circumstances. Actual results could differ from those estimates. Changes in estimates are reflected in reported results in the period in which they become known.

Revenue Recognition

We recognize revenue when a customer obtains control of promised goods or services. We record the amount of revenue that reflects the consideration that we expect to receive in exchange for those goods or services. We apply the following five-step model in order to determine this amount: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations, including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations; and (v) recognition of revenue when (or as) we satisfy each performance obligation.

We only apply the five-step model to contracts when it is probable that we will collect the consideration to which we are entitled in exchange for the goods or services that we transfer to the customer. Once a contract is determined to be within the scope of Accounting Standards Codification ("ASC") 606, *Revenue from Contracts with Customers* ("ASC 606") at contract inception, we review the contract to determine which performance obligations we must deliver and which of these performance obligations are distinct. We recognize as revenue the amount of the transaction price that is allocated to each performance obligation when that performance obligation is satisfied or as it is satisfied. Generally, our performance obligations are transferred to customers at a point in time, typically upon delivery.

Product Revenues, Net

We sell our products principally to a limited number of specialty pharmacy and specialty distributors in the United States ("U.S."), which account for the largest portion of our total revenues. We make international sales primarily to specialty

distributors and retail chains, as well as hospitals and clinics, many of which are government-owned or supported. Our customers in the U.S. subsequently resell the products to patients and health care providers. We recognize net product revenues from sales when our customers obtain control of our products, which typically occurs upon delivery to our customers. Our payment terms are approximately 30 days in the U.S. and consistent with prevailing practice in international markets.

Revenues from product sales are recorded at the net sales price, or "transaction price," which includes estimates of variable consideration that result from (a) invoice discounts for prompt payment and distribution fees, (b) government and private payor rebates, chargebacks, discounts and fees and (c) costs of co-pay assistance programs for patients, as well as other incentives for certain indirect customers. Reserves are established for the estimates of variable consideration based on the amounts earned or to be claimed on the related sales. The reserves are classified as reductions to "Accounts receivable, net" if payable to a customer or "Accrued expenses" if payable to a third-party. Where appropriate, we utilize the expected value method to determine the appropriate amount for estimates of variable consideration based on factors such as our historical experience, current contractual and statutory requirements, specific known market events and trends, industry data and forecasted customer buying and payment patterns. The amount of variable consideration that is included in the transaction price may be constrained and is included in net product revenues only to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period. Actual amounts of consideration ultimately received may differ from our estimates. If actual results vary from our estimates, we adjust these estimates, which would affect net product revenue and earnings in the period such variances become known.

Invoice Discounts and Distribution Fees: We generally provide invoice discounts on product sales to our customers for prompt payment and pays fees for distribution services, such as fees for certain data that customers provide to us. We estimate that, based on our experience, our customers will earn these discounts and fees, and deduct the full amount of these discounts and fees from our gross product revenues and accounts receivable at the time such revenues are recognized.

Rebates, Chargebacks, Discounts and Fees: We contract with government agencies (our "Third-party Payors") so that products will be eligible for purchase by, or partial or full reimbursement from, such Third-party Payors. We estimate the rebates, chargebacks, discounts and fees we will provide to Third-party Payors and deduct these estimated amounts from our gross product revenues at the time the revenues are recognized. For each product, we estimate the aggregate rebates, chargebacks and discounts that we will provide to Third-party Payors based upon (i) our contracts with these Third-party Payors, (ii) the government-mandated discounts and fees applicable to government-funded programs, (iii) information obtained from our customers and other third-party data regarding the payor mix for such product and (iv) historical experience.

Other Incentives: Other incentives that we offer include co-pay mitigation rebates that we provide to commercially insured patients who have coverage and who reside in states that permit co-pay mitigation programs. Based upon the terms of our co-pay mitigation programs, we estimate average co-pay mitigation amounts for each of our products in order to establish appropriate accruals.

We make significant estimates and judgments that materially affect our recognition of net product revenues. We adjust our estimated rebates, chargebacks and discounts based on new information, including information regarding actual rebates, chargebacks and discounts for our products, as it becomes available. Claims by third-party payors for rebates, chargebacks and discounts frequently are submitted to us significantly after the related sales, potentially resulting in adjustments in the period in which the new information becomes known. Our credits to product revenue related to prior period sales have not been significant and primarily related to rebates and discounts.

We exclude taxes collected from customers relating to product sales and remitted to governmental authorities from revenues.

Contract Liabilities

We recorded contract liabilities of $171.7 million and $191.5 million as of December 31, 2021 and 2020, respectively, related to annual contracts with government-owned and supported customers in international markets that limit the amount of annual reimbursement we can receive. Upon exceeding the annual reimbursement amount, products are provided free of

charge, which is a material right. These contracts include upfront payments and fees. We defer a portion of the consideration received for shipments made up to the annual reimbursement limit as a portion of "Other current liabilities." The deferred amount is recognized as revenue when the free products are shipped. Our product revenue contracts include performance obligations that are one year or less.

Our contract liabilities at the end of each fiscal year relate to contracts with annual reimbursement limits in international markets in which the annual period associated with the contract is not the same as our fiscal year. In these markets we recognize revenues related to performance obligations satisfied in previous years; however, these revenues do not relate to any performance obligations that were satisfied more than 12 months prior to the beginning of the current year. During the years ended December 31, 2021, 2020 and 2019, we recorded $191.5 million, $62.3 million and $24.9 million, respectively, of revenues that were recorded as contract liabilities at the beginning of the year.

French Early Access Programs

In 2015, we began distributing ORKAMBI through early access programs in France and remained engaged in reimbursement discussions with the French government until November 2019, when we reached an agreement with the French government for ORKAMBI, including ORKAMBI distributed through early access programs. From the time we began distributing ORKAMBI through early access programs in France, we expected the difference between the amounts collected based on the invoiced amount and the final amount for ORKAMBI distributed through early access programs would be returned to the French government.

Through the third quarter of 2019, we recognized net product revenues for ORKAMBI sales in France under the early access programs based on a transaction price that reflected our estimate of consideration we expected to retain that would not be subject to a significant reversal in amounts recognized. When determining if variable consideration should be constrained, we consider whether there are factors outside our control that could result in a significant reversal of revenue. In making these assessments, we consider the likelihood and magnitude of a potential reversal of revenue.

Upon reaching an agreement with the French government for ORKAMBI, including ORKAMBI distributed through early access programs in November 2019, we updated the transaction price to reflect the final amount for ORKAMBI distributed through early access programs. As a result, we recognized net product revenues of $155.8 million related to prior period ORKAMBI early access program sales in the fourth quarter of 2019 because the updated transaction price for ORKAMBI distributed through these programs exceeded our previous estimate of the consideration we expected to retain that would not be subject to a significant reversal in amounts recognized. We paid the final amount due to the French government in 2020.

Other Revenues

We have not recorded significant revenues other than our product revenues during the three years ended December 31, 2021; however, in future periods, we may recognize collaborative revenues generated through collaborative research, development and/or commercialization agreements related to one or more of the following: nonrefundable, upfront license fees; development and commercial milestones; funding of research and/or development activities; and royalties on net sales of licensed products. Revenue is recognized upon satisfaction of a performance obligation by transferring control of a good or service to our collaborator.

For each collaborative research, development, and/or commercialization agreement that results in revenue, we identify all material performance obligations and determine the transaction price by estimating the amount of variable consideration at the outset of the contract. We constrain (reduce) the estimate of variable consideration such that it is probable that a significant reversal of previously recognized revenue will not occur throughout the life of the contract.

Once the estimated transaction price is established, amounts are allocated to each separate performance obligation that has been identified on a relative standalone selling price basis.

Upfront License Fees: If we determine that a license to our intellectual property is distinct from the other performance obligations identified in an arrangement, we recognize revenue from the related nonrefundable, upfront license fees based on the relative standalone selling price prescribed to the license compared to the total selling price of

the arrangement. We recognize revenue when the license is transferred to our collaborator and our collaborator is able to use and benefit from the license. For licenses that are not distinct from other obligations identified in the arrangement, we utilize judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time. If the combined performance obligation is satisfied over time, we apply an appropriate method of measuring progress for purposes of recognizing revenue from nonrefundable, upfront license fees. We evaluate the measure of progress each reporting period and, if necessary, adjust the measure of performance and related revenue recognition.

Development and Regulatory Milestone Payments: Depending on facts and circumstances, we may include certain milestones in the estimated transaction price or fully constrain the milestones. We include a milestone payment in the transaction price in the reporting period that it is probable that recording revenue in the period will not result in a significant reversal in amounts recognized in future periods. This may result in us recognizing revenues from certain milestones and a corresponding contract asset in a reporting period before the milestone is achieved. We fully constrain milestone payments that have not been included in the transaction price to date until we conclude that their achievement is probable and that recognition of the related revenue will not result in a significant reversal in amounts recognized in future periods. We re-evaluate the probability of achievement of such development milestones and any related constraint each reporting period and adjust our estimate of the overall transaction price, including the amount of collaborative revenue that we have recorded, if necessary.

Research and Development Activities/Transition Services: If we are entitled to reimbursement from our collaborators for specified research and development expenses, we account for the related services as separate performance obligations if these services represent a material right. We also determine whether to account for the reimbursement of research and development expenses as collaborative revenues or an offset to research and development expenses in accordance with the provisions of gross or net revenue presentation. We recognize the corresponding revenues or record the corresponding offset to research and development expenses as we satisfy the related performance obligations.

Concentration of Credit Risk

Financial instruments that potentially subject us to concentration of credit risk consist principally of money market funds and marketable securities. We place these investments with highly rated financial institutions, and, by policy, limit the amount of credit exposure to any one financial institution. These amounts at times may exceed federally insured limits. We also maintain a foreign currency hedging program that includes foreign currency forward contracts with several counterparties. We have not experienced any credit losses related to these financial instruments and do not believe we are exposed to any significant credit risk related to these instruments.

We are also subject to credit risk from our accounts receivable related to our product sales and collaborators. We evaluate the creditworthiness of each of our customers and have determined that all our material customers are creditworthy. To date, we have not experienced significant losses with respect to the collection of our accounts receivable. We believe that our allowances, which are not significant to our consolidated financial statements, are adequate at December 31, 2021. Please refer to Note Q, “Segment Information,” for further information.

Cash and Cash Equivalents

We consider all highly liquid investments with original maturities of three months or less at the date of purchase to be cash equivalents.

Marketable Securities

As of December 31, 2021, our marketable securities consisted of investments in available-for-sale debt securities and corporate equity securities with readily determinable fair values. We classify marketable securities available to fund current operations as current assets on our consolidated balance sheets. Marketable securities are classified as long-term assets on our consolidated balance sheets if (i) they have been in an unrealized loss position for longer than one year and (ii) we have the ability and intent to hold them (a) until the carrying value is recovered and (b) such holding period may be longer than one year. Our marketable securities are stated at fair value. The fair value of these securities is based on quoted prices for

identical or similar assets.

We record unrealized gains (losses) on available-for-sale debt securities as a component of "Accumulated other comprehensive income (loss)," which is a separate component of shareholders' equity on our consolidated balance sheet, until such gains and losses are realized. Realized gains and losses, if any, are determined using the specific identification method.

We record changes in the fair value of our investments in corporate equity securities to "Other income, net" in our consolidated statements of operations. Realized gains and losses, which are also included in "Other income, net," are determined on an original weighted-average cost basis.

We adopted Accounting Standards Update ("ASU") 2016-13, *Financial Instruments - Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments* ("ASU 2016-13") as of January 1, 2020, which did not have a significant impact on our consolidated financial statements. For available-for-sale debt securities in unrealized loss positions, ASU 2016-13 requires us to record an allowance for credit losses using an expected loss model, which replaces the incurred loss model required under the previous guidance. A credit loss is limited to the amount by which the amortized cost of an investment exceeds its fair value. A previously recognized credit loss may be decreased in subsequent periods if our estimate of fair value for the investment increases. To determine whether to record a credit loss, we consider issuer specific credit ratings and historical losses as well as current economic conditions and our expectations for future economic conditions.

Accounts Receivable

We deduct invoice discounts for prompt payment and fees for distribution services from our accounts receivable based on our experience that our customers will earn these discounts and fees. Our estimates for our allowance for credit losses, which has not been significant to date, is determined based on existing contractual payment terms, historical payment patterns, current economic conditions and our expectation for future economic conditions.

Stock-based Compensation Expense

We expense the fair value of employee restricted stock units and other forms of stock-based employee compensation over the associated employee service period on a straight-line basis. Stock-based compensation expense is determined based on the fair value of the award at the grant date and is adjusted each period to reflect actual forfeitures and the outcomes of certain performance conditions.

For awards with performance conditions in which the award does not vest unless the performance condition is met, we recognize expense if, and to the extent that, we estimate that achievement of the performance condition is probable. If we conclude that vesting is probable, we recognize expense from the date we reach this conclusion through the estimated vesting date.

We provide to employees who have rendered a certain number of years of service to Vertex and meet certain age requirements, partial or full acceleration of vesting of these equity awards, subject to certain conditions including a notification period, upon a termination of employment other than for cause. Approximately 5% of our employees were eligible for partial or full acceleration of any of their equity awards as of December 31, 2021. We recognize stock-based compensation expense related to these awards over a service period reflecting qualified employees' eligibility for partial or full acceleration of vesting.

Please refer to Note N, "Stock-based Compensation Expense," for tables displaying our stock-based compensation expense by type of award and by line item within our consolidated statements of operations.

Research and Development Expenses

Research and development expenses are comprised of costs we incur in performing research and development activities, including salary and benefits; stock-based compensation expense; outsourced services and other direct expenses, including clinical trial and pharmaceutical development costs; collaborative payments; and infrastructure costs, including facilities costs and depreciation expense. We recognize research and development expenses as incurred. We capitalize nonrefundable advance payments we make for research and development activities and expense the payments as the related goods are

delivered or the related services are performed.

Inventories

We value our inventories at the lower-of-cost or net realizable value. We determine the cost of our inventories, which include amounts related to materials and manufacturing overhead, on a first-in, first-out basis. We perform an assessment of the recoverability of our capitalized inventory during each reporting period and write down any excess and obsolete inventories to their net realizable value in the period in which the impairment is first identified. Shipping and handling costs incurred for inventory purchases are capitalized and recorded upon sale in "Cost of sales" in our consolidated statements of operations. Shipping and handling costs incurred for product shipments are recorded as incurred in "Cost of sales" in our consolidated statements of operations.

We capitalize inventories produced in preparation for initiating sales of a product candidate when the related product candidate is considered to have a high likelihood of regulatory approval and the related costs are expected to be recoverable through sales of the inventories. In determining whether to capitalize such inventories, we evaluate, among other factors, information regarding the product candidate's safety and efficacy, the status of regulatory submissions and communications with regulatory authorities and the outlook for commercial sales, including the existence of current or anticipated competitive drugs and the availability of reimbursement. In addition, we evaluate risks associated with manufacturing the product candidate and the remaining shelf-life of the inventories.

Property and Equipment

Property and equipment are recorded at cost, net of accumulated depreciation. Depreciation expense is recorded using the straight-line method over the estimated useful life of the related asset generally as follows:

Description	Estimated Useful Life
Buildings and improvements	15 to 40 years
Furniture and equipment	7 to 10 years
Leasehold improvements; assets under finance leases	The shorter of the useful life of the assets or the estimated remaining term of the associated lease
Computers and software	3 to 5 years

Maintenance and repairs to an asset that do not improve or extend its life are charged to operations. When assets are retired or otherwise disposed of, the assets and related accumulated depreciation are eliminated from the accounts and any resulting gain or loss is reflected in our consolidated statements of operations. We perform an assessment of the fair value of the assets if indicators of impairment are identified during a reporting period and record the assets at the lower of the net book value or the fair value of the assets.

We capitalize internal costs incurred to develop software for internal use during the application development stage. Amortization of capitalized internally developed software costs is recorded in depreciation expense over the useful life of the related asset.

Leases

We determine whether an arrangement contains a lease at inception. If a lease is identified in an arrangement, we recognize a right-of-use asset and liability on our consolidated balance sheet and determine whether the lease should be classified as a finance or operating lease. We do not recognize assets or liabilities for leases with lease terms of less than 12 months.

A lease qualifies as a finance lease if any of the following criteria are met at the inception of the lease: (i) there is a transfer of ownership of the leased asset to Vertex by the end of the lease term, (ii) we hold an option to purchase the leased asset that we are reasonably certain to exercise, (iii) the lease term is for a major part of the remaining economic life of the leased asset, (iv) the present value of the sum of lease payments equals or exceeds substantially all of the fair value of the leased asset, or (v) the nature of the leased asset is specialized to the point that it is expected to provide the lessor no

alternative use at the end of the lease term. All other leases are recorded as operating leases.

Finance and operating lease assets and liabilities are recognized at the lease commencement date based on the present value of the lease payments over the lease term using the discount rate implicit in the lease. If the rate implicit is not readily determinable, we utilize our incremental borrowing rate at the lease commencement date. Operating lease assets are further adjusted for prepaid or accrued lease payments. Operating lease payments are expensed using the straight-line method as an operating expense over the lease term. Finance lease assets are amortized to depreciation expense using the straight-line method over the shorter of the useful life of the related asset or the lease term. Finance lease payments are bifurcated into (i) a portion that is recorded as imputed interest expense and (ii) a portion that reduces the finance liability associated with the lease.

We do not separate lease and non-lease components when determining which lease payments to include in the calculation of our lease assets and liabilities. Variable lease payments are expensed as incurred. If a lease includes an option to extend or terminate the lease, we reflect the option in the lease term if it is reasonably certain we will exercise the option.

Finance leases are recorded in “Property and equipment, net,” “Other current liabilities” and “Long-term finance lease liabilities,” and operating leases are recorded in “Operating lease assets,” “Other current liabilities” and “Long-term operating lease liabilities” on our consolidated balance sheet.

Income Taxes

Deferred tax assets and liabilities are recognized for the expected future tax consequences of temporary differences between the financial statement carrying amounts and the income tax bases of assets and liabilities. A valuation allowance is applied against any net deferred tax asset if, based on the available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized. On a periodic basis, we reassess the valuation allowance on our deferred income tax assets weighing positive and negative evidence to assess the recoverability of our deferred tax assets. We include, among other things, our recent financial performance and our future projections in this periodic assessment.

We record liabilities related to uncertain tax positions by prescribing a minimum recognition threshold and measurement attribute for the financial statement recognition and measurement of a tax position taken or expected to be taken in a tax return. We evaluate our uncertain tax positions on a quarterly basis and consider various factors, including, but not limited to, changes in tax law, the measurement of tax positions taken or expected to be taken in our tax returns, and changes in facts or circumstances related to a tax position. We adjust our liabilities to reflect any subsequent changes in the relevant facts and circumstances surrounding the uncertain positions. We accrue interest and penalties related to unrecognized tax benefits as a component of our “Provision for income taxes.”

As part of the U.S. Tax Cut and Jobs Act of 2017, we are subject to a territorial tax system, under which we must establish an accounting policy to provide for tax on Global Intangible Low Taxed Income (“GILTI”) earned by certain foreign subsidiaries. We have elected to treat the impact of GILTI as a current tax expense in our “Provision for income taxes.”

Variable Interest Entities

We review each collaboration agreement pursuant to which we license assets owned by a collaborator in order to determine whether or not we have a variable interest via the license agreement with our collaborator and if the variable interest is a variable interest in our collaborator as a whole and whether or not we are the primary beneficiary of that variable interest entity (“VIE”). If we determine we are the primary beneficiary of a VIE at the onset of our collaboration agreement, the collaboration is treated as a business combination and we consolidate the financial statements of the VIE into our consolidated financial statements until we are no longer the primary beneficiary of the consolidated VIE, or no longer have a variable interest in the VIE. As of December 31, 2021 and 2020, we did not have any consolidated VIEs.

Fair Value of In-process Research and Development Assets and Contingent Payments

The present-value models we use to estimate the fair values of in-process research and development assets and contingent payments pursuant to collaborations and acquisitions incorporate significant assumptions.

Our discounted cash flow models pertaining to in-process research and development assets include: (i) assumptions regarding the probability of obtaining marketing approval for a product candidate; (ii) the timing of and the expected costs to develop and commercialize a product candidate; (iii) estimates of future cash flows from potential product sales with respect to a product candidate; and (iv) appropriate discount and tax rates.

We base our estimates of the probability of achieving the milestones relevant to the fair value of contingent payments, which could include milestone, royalty and option payments, on industry data. Estimates included in the discounted cash flow models pertaining to contingent payments also include: (i) estimate regarding the timing of the relevant development and commercial milestones and royalties, (ii) and appropriate discount rates. We record any increases or decreases in the fair value of our contingent payments as charges or credits to "Change in fair value of contingent consideration" in our consolidated statement of operations. Please refer to Note D, "Fair Value Measurements," for further information.

In-process Research and Development Assets

We record the fair value of in-process research and development assets as of the transaction date of a business combination. Each of these assets is accounted for as an indefinite-lived intangible asset and is maintained on our consolidated balance sheet until either the underlying project is completed or the asset becomes impaired. If the asset becomes impaired or is abandoned, the carrying value of the related intangible asset is written down to its fair value, and an impairment charge is recorded in the period in which the impairment occurs. If a project is completed, the carrying value of the related intangible asset is amortized as a part of "Cost of sales" over the remaining estimated life of the asset beginning in the period in which the project is completed. In-process research and development assets are tested for impairment on an annual basis as of October 1, and more frequently if indicators are present or changes in circumstances suggest that impairment may exist.

In-process research and development that is acquired in a transaction that does not qualify as a business combination under U.S. GAAP and that does not have an alternative future use is recorded to "Research and development expenses" in the period in which it is acquired.

Goodwill

The difference between the purchase price and the fair value of assets acquired and liabilities assumed in a business combination is allocated to goodwill. Goodwill is evaluated for impairment on an annual basis as of October 1, and more frequently if indicators are present or changes in circumstances suggest that impairment may exist. As noted in *Basis of Presentation* above, we have one operating segment, pharmaceuticals, which is our only reporting unit.

Hedging Activities

We recognize the fair value of hedging instruments that are designated and qualify as hedging instruments pursuant to U.S. GAAP, foreign currency forward contracts, as either assets or liabilities on our consolidated balance sheets. Changes in the fair value of these instruments are recorded each period in "Accumulated other comprehensive income (loss)" as unrealized gains and losses until the forecasted underlying transaction occurs. Unrealized gains and losses on these foreign currency forward contracts are included in "Prepaid expenses and other current assets" or "Other assets," and "Other current liabilities" or "Other long-term liabilities," respectively, on our consolidated balance sheets depending on the remaining period until their contractual maturity. Realized gains and losses for the effective portion of such contracts are recognized in "Product revenues, net" in our consolidated statement of operations in the same period that we recognize the product revenues that were impacted by the hedged foreign exchange rate changes. We classify the cash flows from hedging instruments in the same category as the cash flows from the hedged items.

Certain of our hedging instruments are subject to master netting arrangements to reduce the risk arising from such transactions with our counterparties. We present unrealized gains and losses on our foreign currency forward contracts on a gross basis within our consolidated balance sheets.

We also enter into foreign currency forward contracts with contractual maturities of less than one month designed to mitigate the effect of changes in foreign exchange rates on monetary assets and liabilities including intercompany balances. These contracts are not designated as hedging instruments pursuant to U.S. GAAP. Realized gains and losses for such

contracts are recognized in “Other income, net” in our consolidated statement of operations each period.

Comprehensive Income

Comprehensive income consists of net income and other comprehensive income (loss), which includes foreign currency translation adjustments and unrealized gains and losses on foreign currency forward contracts and certain marketable securities. For purposes of comprehensive income disclosures, we record provisions for or benefits from income taxes related to the unrealized gains and losses on foreign currency forward contracts and certain marketable securities. We do not record provisions for or benefits from income taxes related to our cumulative translation adjustment, as we intend to permanently reinvest undistributed earnings in our foreign subsidiaries.

Foreign Currency Translation and Transactions

The majority of our operations occur in entities that have the U.S. dollar denominated as their functional currency. The assets and liabilities of our entities with functional currencies other than the U.S. dollar are translated into U.S. dollars at exchange rates in effect at the end of the year. Revenue and expense amounts for these entities are translated using the average exchange rates for the period. Net unrealized gains and losses resulting from foreign currency translation are included in “Accumulated other comprehensive income (loss).” Net foreign currency exchange transaction losses, which are included in “Other income, net” on our consolidated statement of operations, were $13.9 million, $16.1 million and $5.2 million for 2021, 2020 and 2019, respectively. These net foreign currency exchange losses are presented net of the impact of the foreign currency forward contracts designed to mitigate their effect on our consolidated statement of operations.

Share Repurchase Programs

Repurchases of our common stock are recorded as reductions to “Common Stock” and “Additional paid-in capital” pursuant to our established accounting policy. Repurchases in excess of the par value will be recorded as reductions to “Retained earnings” in the event that “Additional paid-in capital” is reduced to zero.

Net Income Per Common Share

Basic net income per common share is based upon the weighted-average number of common shares outstanding during the period. Diluted net income per common share utilizing the treasury-stock method is based upon the weighted-average number of common shares outstanding during the period plus additional weighted-average common equivalent shares outstanding during the period when the effect is dilutive. Potentially dilutive shares result from the assumed exercise of outstanding stock options and assumed vesting of restricted stock units (including performance-based restricted stock units) (the proceeds of which are then assumed to have been used to repurchase outstanding stock using the treasury-stock method).

Recently Adopted Accounting Standards

Income Taxes

In 2019, the Financial Accounting Standards Board (“FASB”) issued ASU 2019-12, *Income Taxes (Topic 740)* (“ASU 2019-12”), which simplifies the accounting for income taxes. ASU 2019-12 became effective on January 1, 2021. The adoption of ASU 2019-12 did not have a significant impact on our consolidated financial statements.

Internal-Use Software

In 2018, the FASB issued ASU 2018-15, *Intangibles—Goodwill and Other—Internal-Use Software (Subtopic 350-40): Customer’s Accounting for Implementation Costs Incurred in a Cloud Computing Arrangement That Is a Service Contract* (“ASU 2018-15”), which clarifies the accounting for implementation costs in cloud computing arrangements. ASU 2018-15 became effective on January 1, 2020. The adoption of ASU 2018-15 resulted in an insignificant amount of additional assets recorded on our consolidated balance sheet.

Fair Value Measurement

In 2018, the FASB issued ASU 2018-13, *Fair Value Measurement (Topic 820): Disclosure Framework-Changes to the Disclosure Requirements for Fair Value Measurement* (“ASU 2018-13”), which modifies the disclosure requirements for fair

value measurements. ASU 2018-13 became effective on January 1, 2020. The adoption of ASU 2018-13 resulted in additional disclosures related to our Level 3 inputs. Please refer to Note D, “Fair Value Measurements,” for further information.

Credit Losses

In 2016, the FASB issued ASU 2016-13, which requires entities to record expected credit losses for certain financial instruments, including trade receivables, as an allowance that reflects the entity's current estimate of credit losses expected to be incurred. For available-for-sale debt securities in unrealized loss positions, ASU 2016-13 requires allowances to be recorded instead of reducing the amortized cost of the investment. ASU 2016-13 became effective on January 1, 2020. The adoption of ASU 2016-13 did not have a significant impact on our consolidated financial statements.

Leases

On January 1, 2019, we adopted ASC 842 using the modified-retrospective method. Until December 31, 2018, we applied build-to-suit accounting and were the deemed owner of our leased corporate headquarters in Boston and research site in San Diego. Under the amended guidance that became effective January 1, 2019, we account for these buildings as finance leases. As of January 1, 2019, we recorded a cumulative effect adjustment to increase our “Accumulated deficit” by $40.3 million to reflect our build-to-suit leases as finance leases pursuant to ASC 842.

Recently Issued Accounting Standards

We do not expect any recently issued accounting standards to have a significant impact on our consolidated financial statements.

B. Collaborative and Other Arrangements

We have entered into numerous agreements pursuant to which we collaborate with third parties on research, development and commercialization programs, including in-license and out-license agreements or acquire assets. Our “Research and development expenses” included $1.1 billion, $184.6 million and $318.3 million related to upfront and milestone payments pursuant to our in-license agreements and asset acquisitions in 2021, 2020 and 2019, respectively.

In-license Agreements

We have entered into a number of in-license agreements in order to advance and obtain access to technologies and services related to our research and early-development activities. We are generally required to make an upfront payment upon execution of our license agreements; development, regulatory and commercialization milestones payments upon the achievement of certain product research, development and commercialization objectives; and royalty payments on future sales, if any, of commercial products resulting from our collaborations.

Pursuant to the terms of our in-license agreements, our collaborators typically lead the discovery efforts and we lead all preclinical, development and commercialization activities associated with the advancement of any product candidates and fund all expenses.

We typically can terminate our in-license agreements by providing advance notice to our collaborators; the required length of notice is dependent on whether any product developed under the license agreement has received marketing approval. Our license agreements may be terminated by either party for a material breach by the other, subject to notice and cure provisions. Unless earlier terminated, these license agreements generally remain in effect until the date on which the royalty term and all payment obligations with respect to all products in all countries have expired.

CRISPR Therapeutics AG

CRISPR-Cas9 Gene-editing Therapies

In 2015, we entered into a strategic collaboration, option and license agreement (the “CRISPR Agreement”) with CRISPR Therapeutics AG and its affiliates (“CRISPR”) to collaborate on the discovery and development of potential new

treatments aimed at the underlying genetic causes of human diseases using CRISPR-Cas9 gene-editing technology. We had the exclusive right to license certain targets. In 2019, we paid an aggregate of $30.0 million to exclusively license three targets, including CF, pursuant to the CRISPR Agreement. We recorded the $30.0 million total option payment to "Research and development expenses." For each of the three targets that we elected to license, CRISPR has the potential to receive up to an additional $410.0 million in development, regulatory and commercial milestones as well as royalties on net product sales.

In 2017, we entered into a joint development and commercialization agreement with CRISPR pursuant to the terms of the CRISPR Agreement (the "Original CTX001 JDCA"), under which we and CRISPR were co-developing and preparing to co-commercialize CTX001 for the treatment of hemoglobinopathies, including treatments for sickle cell disease and transfusion-dependent beta thalassemia.

In the second quarter of 2021, we and CRISPR amended and restated the Original CTX001 JDCA (the "A&R JDCA"), pursuant to which the parties agreed to, among other things, (a) adjust the governance structure for the collaboration and adjust the responsibilities of each party thereunder; (b) adjust the allocation of net profits and net losses between the parties; and (c) exclusively license (subject to CRISPR's reserved rights to conduct certain activities) certain intellectual property rights to us relating to the products that may be researched, developed, manufactured and commercialized under such agreement.

Pursuant to the A&R JDCA, we are now leading global development, manufacturing and commercialization of CTX001, with support from CRISPR. Subject to the terms and conditions of the A&R JDCA, we also have the right to conduct all research, development, manufacturing and commercialization activities relating to the product candidates and products under the A&R JDCA (including CTX001) throughout the world subject to CRISPR's reserved right to conduct certain activities.

In connection with the A&R JDCA, we made a $900.0 million upfront payment to CRISPR in the second quarter of 2021. We concluded that we did not have any alternative future use for the acquired in-process research and development and recorded this upfront payment to "Research and development expenses." CRISPR has the potential to receive an additional one-time $200.0 million milestone payment upon receipt of the first marketing approval of CTX001 from the U.S. Food and Drug Administration or the European Commission.

We and CRISPR shared equally all expenses incurred under the Original CTX001 JDCA. On July 1, 2021, with respect to CTX001, the net profits and net losses incurred pursuant to the A&R JDCA began to be allocated 60% to us and 40% to CRISPR, while all other product candidates and products continue to have net profits and net losses shared equally between the parties. We concluded that the Original CTX001 JDCA and the A&R JDCA are cost-sharing arrangements, which result in the net impact of the arrangements being recorded in "Research and development expenses" in our consolidated statements of operations. During the three years ended December 31, 2021, we recognized the following amounts in total related to these agreements:

	2021	2020	2019
	(in millions)		
Total research and development expenses incurred under the Original CTX001 JDCA and A&R JDCA	$ 230.4	$ 101.2	$ 60.3
Vertex's share recognized in "Research and development expenses" in consolidated statements of operations	129.0	50.6	30.1

Duchenne Muscular Dystrophy and Myotonic Dystrophy Type 1

In 2019, we entered into a separate strategic collaboration and license agreement (the "CRISPR DMD/DM1 Agreement") with CRISPR. Pursuant to this agreement, we received an exclusive worldwide license to CRISPR's existing and future intellectual property for Duchenne muscular dystrophy ("DMD") and myotonic dystrophy type 1 ("DM1") and we made an upfront payment of $175.0 million to CRISPR. We concluded that we did not have any alternative future use for the acquired in-process research and development and recorded the upfront payment to "Research and development expenses." We recorded $12.5 million and $25.0 million to "Research and development expenses" in 2021 and 2020, respectively, related to pre-clinical milestones earned by CRISPR under the CRISPR DMD/DM1 Agreement. CRISPR has the potential to receive up to an additional $787.5 million in research, development, regulatory and commercial milestones for the DMD and

DM1 programs as well as royalties on net product sales. CRISPR has the option to co-develop and co-commercialize all DM1 products globally and forego the milestones and royalties associated with the DM1 program. We fund all expenses associated with the collaboration.

Kymera Therapeutics Inc.

In 2019, we entered into a strategic research and development collaboration agreement with Kymera Therapeutics Inc. ("Kymera") to advance small molecule protein degraders against multiple targets. Kymera's proprietary platform technology is being applied in the collaboration activities in exchange for an upfront payment of $50.0 million. We have the exclusive right to license up to six protein targets, for each of which Kymera may receive up to $170.0 million in payments, including development, regulatory and commercial milestones as well as royalties on net product sales. We determined that substantially all of the fair value of the Kymera collaboration agreement was attributable to in-process research and development and no substantive processes were acquired that would constitute a business. We concluded that we did not have any alternative future use for the acquired in-process research and development and recorded the $50.0 million upfront payment to "Research and development expenses."

In addition to the upfront payment, we purchased $20.0 million of Kymera's preferred stock that converted to common stock when Kymera became a publicly traded company in 2020.

Moderna, Inc.

In 2016, we entered into a strategic collaboration and licensing agreement with Moderna, Inc. ("Moderna"), pursuant to which the parties are seeking to identify and develop messenger ribonucleic acid ("mRNA") therapeutics for the treatment of CF.

In 2020, we entered into a new strategic collaboration and licensing agreement with Moderna (the "2020 Moderna Agreement") aimed at the discovery and development of lipid nanoparticles and mRNAs that can deliver gene-editing therapies to lung cells for the treatment of CF. Pursuant to the 2020 Moderna Agreement, we paid Moderna an upfront payment of $75.0 million and Moderna is eligible to receive up to $380.0 million in development, regulatory and commercial milestones as well as royalties on net product sales. We determined that substantially all the fair value of the 2020 Moderna Agreement was attributable to in-process research and development and no substantive processes were acquired that would constitute a business. We concluded that we did not have any alternative future use for the acquired in-process research and development and recorded the upfront payment to "Research and development expenses."

Additional In-License Agreements and Other Arrangements

In 2016, we entered into a strategic collaboration and license agreement with ApoLo1 Bio, LLC ("ApoLo1") related to our drug discovery efforts in APOL1-mediated kidney disease. In 2021, based on positive results from a Phase 2 proof-of-concept study of VX-147 in patients with APOL1-mediated focal segmental glomerulosclerosis, we paid ApoLo1 a $15.0 million milestone and exercised our $60.0 million option to buy-out all future development milestones, regulatory milestones and future royalties on net product sales. We recorded these payments to "Research and development expenses" because we concluded that we did not have any alternative future use for the acquired in-process research and development.

In addition to the collaborative arrangements described above, we recorded upfront, option and milestone payments totaling $125.8 million in 2021, $84.6 million in 2020 and $63.3 million in 2019 to "Research and development expenses" related to additional in-license agreements and other business development transactions that we do not consider to be individually significant to our consolidated financial statements. These payments included upfront payments of $31.0 million to Mammoth Biosciences, Inc. ("Mammoth") and $25.0 million to Arbor Biotechnologies, Inc. ("Arbor") in 2021, $40.0 million to Skyhawk Therapeutics, Inc. ("Skyhawk") in 2020, and $25.9 million to Molecular Templates, Inc. ("Molecular") in 2019.

For Mammoth, Arbor, Skyhawk, Molecular and several other in-license agreements that are not individually significant to our consolidated financial statements, we determined that substantially all the fair value of each individual agreement was attributable to in-process research and development and no substantive processes were acquired that would constitute a business. We concluded that we did not have any alternative future use for the acquired in-process research and development

associated with the agreements and recorded the upfront payments for these agreements to “Research and development expenses.” Please refer to Note D, “Fair Value Measurements,” and Note E, “Marketable Securities and Equity Investments,” for further information regarding our investments in our collaborators.

Out-license Agreements

We have entered into licensing agreements pursuant to which we have out-licensed rights to certain product candidates to third-party collaborators. Pursuant to these out-license agreements, our collaborators become responsible for all costs related to the continued development of such product candidates and obtain development and commercialization rights to these product candidates. Depending on the terms of the agreements, our collaborators may be required to make upfront payments, milestone payments upon the achievement of certain product research and development objectives and may also be required to pay royalties on future sales, if any, of commercial products resulting from the collaboration. The termination provisions associated with these collaborations are generally the same as those described above related to our in-license agreements.

Merck KGaA, Darmstadt, Germany

In 2017, we entered into a strategic collaboration and license agreement (the “Oncology Agreement”) with Merck KGaA, Darmstadt, Germany (the “Licensee”). Pursuant to the Oncology Agreement, we granted the Licensee an exclusive worldwide license to research, develop and commercialize four oncology research and development programs including two clinical-stage programs targeting DNA damage repair: our ataxia telangiectasia and Rad3-related protein kinase inhibitor program, or ATR program, including VX-970 and VX-803, and our DNA-dependent protein kinase inhibitor program, or DNA-PK program, including VX-984. In addition, we granted the Licensee exclusive, worldwide rights to two pre-clinical programs.

In 2018, we entered into an agreement with Merck KGaA, Darmstadt, Germany (the “DNA-PK Agreement”) whereby we licensed the two lead Vertex DNA-PK compounds from our DNA-PK program for use in the field of gene integration for six specific indications. Merck KGaA, Darmstadt, Germany has the potential to receive additional milestones, primarily related to approval and reimbursement in various markets, as well as royalties on net product sales.

Cystic Fibrosis Foundation

We have a research, development and commercialization agreement that was originally entered into in 2004 with the Cystic Fibrosis Foundation, as successor in interest to the Cystic Fibrosis Foundation Therapeutics, Inc. This agreement was most recently amended in 2016. Pursuant to the agreement, as amended, we agreed to pay royalties ranging from low-single digits to mid-single digits on potential sales of certain compounds first synthesized and/or tested between March 1, 2014 and August 31, 2016, including elexacaftor, and tiered royalties ranging from single digits to sub-teens on covered compounds first synthesized and/or tested during a research term on or before February 28, 2014, including KALYDECO (ivacaftor), ORKAMBI (lumacaftor in combination with ivacaftor) and SYMDEKO/SYMKEVI (tezacaftor in combination with ivacaftor). For combination products, such as ORKAMBI, SYMDEKO/SYMKEVI and TRIKAFTA/KAFTRIO (elexacaftor/tezacaftor/ivacaftor and ivacaftor), sales are allocated equally to each of the active pharmaceutical ingredients in the combination product. We record our royalties payable to the Cystic Fibrosis Foundation to “Cost of sales.”

C. Earnings Per Share

The following table sets forth the computation of basic and diluted net income per common share for the periods ended:

	2021	2020	2019
	(in millions, except per share amounts)		
Net income	$ 2,342.1	$ 2,711.7	$ 1,176.8
Basic weighted-average common shares outstanding	257.7	259.8	256.7
Effect of potentially dilutive securities:			
Stock options	1.1	1.8	2.2
Restricted stock units (including PSUs)	1.1	1.7	1.7
Employee stock purchase program	0.0	0.1	0.1
Diluted weighted-average common shares outstanding	259.9	263.4	260.7
Basic net income per common share	$ 9.09	$ 10.44	$ 4.58
Diluted net income per common share	$ 9.01	$ 10.29	$ 4.51

We did not include the securities in the following table in the computation of the diluted net income per common share because the effect would have been anti-dilutive during each period:

	2021	2020	2019
		(in millions)	
Stock options	0.7	0.3	2.8
Unvested restricted stock units (including PSUs)	0.4	0.3	—

D. Fair Value Measurements

The following fair value hierarchy is used to classify assets and liabilities based on observable inputs and unobservable inputs used in order to determine the fair value of our financial assets and liabilities:

Level 1:	Quoted prices in active markets for identical assets or liabilities. An active market for an asset or liability is a market in which transactions for the asset or liability occur with sufficient frequency and volume to provide pricing information on an ongoing basis.
Level 2:	Observable inputs other than Level 1 inputs. Examples of Level 2 inputs include quoted prices in active markets for similar assets or liabilities and quoted prices for identical assets or liabilities in markets that are not active.
Level 3:	Unobservable inputs based on our assessment of the assumptions that market participants would use in pricing the asset or liability.

Our investment strategy is focused on capital preservation. We invest in instruments that meet the credit quality standards outlined in our investment policy, which also limits the amount of credit exposure to any one issue or type of instrument. We maintain strategic investments separately from the investment policy that governs our other cash, cash equivalents and marketable securities as described in Note E, “Marketable Securities and Equity Investments.” Additionally, we utilize foreign currency forward contracts intended to mitigate the effect of changes in foreign exchange rates on our consolidated statement of operations.

During the three years ended December 31, 2021, we did not record any other-than-temporary impairment charges related to our financial assets.

The following tables set forth our financial assets and liabilities subject to fair value measurements by level within the fair value hierarchy (and does not include $3.3 billion and $2.8 billion of cash as of December 31, 2021 and 2020, respectively):

	As of December 31, 2021				As of December 31, 2020			
		Fair Value Hierarchy				Fair Value Hierarchy		
	Total	Level 1	Level 2	Level 3	Total	Level 1	Level 2	Level 3
	(in millions)							
Financial instruments carried at fair value (asset position):								
Cash equivalents:								
Money market funds	$ 3,478.1	$ 3,478.1	$ —	$ —	$ 3,141.1	$ 3,141.1	$ —	$ —
Marketable securities:								
Corporate equity securities	230.9	230.9	—	—	195.8	15.7	180.1	—
U.S. Treasury securities	86.4	86.4	—	—	—	—	—	—
Government-sponsored enterprise securities	69.0	69.0	—	—	80.0	80.0	—	—
Corporate debt securities	90.9	—	90.9	—	231.6	—	231.6	—
Commercial paper	252.7	—	252.7	—	163.3	—	163.3	—
Prepaid expenses and other current assets:								
Foreign currency forward contracts	44.5	—	44.5	—	—	—	—	—
Other assets:								
Foreign currency forward contracts	2.0	—	2.0	—	—	—	—	—
Total financial assets	$ 4,254.5	$ 3,864.4	$ 390.1	$ —	$ 3,811.8	$ 3,236.8	$ 575.0	$ —
Financial instruments carried at fair value (liability position):								
Other current liabilities:								
Foreign currency forward contracts	$ (5.6)	$ —	$ (5.6)	$ —	$ (59.2)	$ —	$ (59.2)	$ —
Long-term contingent consideration	(186.5)	—	—	(186.5)	(189.6)	—	—	(189.6)
Other long-term liabilities:								
Foreign currency forward contracts	(2.7)	—	(2.7)	—	(4.3)	—	(4.3)	—
Total financial liabilities	$ (194.8)	$ —	$ (8.3)	$ (186.5)	$ (253.1)	$ —	$ (63.5)	$ (189.6)

Please refer to Note E, “Marketable Securities and Equity Investments,” for the carrying amount and related unrealized gains (losses) by type of investment.

Fair Value of Corporate Equity Securities

We classify our investments in publicly traded corporate equity securities as “Marketable securities” on our consolidated balance sheets. Generally, our investments in the common stock of publicly traded companies are valued based on Level 1 inputs because they have readily determinable fair values. However, certain of our investments in publicly traded companies have been or continue to be valued based on Level 2 inputs due to transfer restrictions associated with these investments. Please refer to Note E, “Marketable Securities and Equity Investments,” for further information on these investments.

Fair Value of Contingent Consideration

In 2019, we acquired Exonics Therapeutics, Inc. (“Exonics”), a privately-held company focused on creating transformative gene-editing therapies to repair mutations that cause DMD and other severe neuromuscular diseases, including DM1. Our Level 3 contingent consideration liabilities are related to $678.3 million of development and regulatory milestones potentially payable to Exonics’ former equity holders. We base our estimates of the probability of achieving the milestones relevant to the fair value of contingent payments on industry data attributable to rare diseases. The discount rates used in the valuation model for contingent payments, which were between 0.9% and 2.3% as of December 31, 2021, represent a measure of credit risk and market risk associated with settling the liabilities. Significant judgment is used in determining the appropriateness of these assumptions at each reporting period. Due to the uncertainties associated with development and commercialization of product candidates in the pharmaceutical industry and the effects of changes in other assumptions

including discount rates, we expect our estimates regarding the fair value of contingent consideration to change in the future, resulting in adjustments to the fair value of our contingent consideration liabilities, and the effect of any such adjustments could be material.

The following table represents a rollforward of the fair value of our contingent consideration liabilities:

	Year Ended December 31, 2021
	(in millions)
Balance at December 31, 2020	$ 189.6
Decrease in fair value of contingent payments	(3.1)
Balance at December 31, 2021	$ 186.5

E. Marketable Securities and Equity Investments

A summary of our cash equivalents and marketable securities, which are recorded at fair value (and do not include $3.3 billion and $2.8 billion of cash as of December 31, 2021 and 2020, respectively), is shown below:

	As of December 31, 2021				As of December 31, 2020			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
	(in millions)							
Cash equivalents:								
Money market funds	$ 3,478.1	$ —	$ —	$ 3,478.1	$ 3,141.1	$ —	$ —	$ 3,141.1
Marketable securities:								
U.S. Treasury securities	$ 86.6	$ —	$ (0.2)	$ 86.4	$ —	$ —	$ —	$ —
Government-sponsored enterprise securities	69.0	—	—	69.0	80.0	—	—	80.0
Corporate debt securities	91.1	—	(0.2)	90.9	231.3	0.4	(0.1)	231.6
Commercial paper	252.8	—	(0.1)	252.7	163.3	—	—	163.3
Total marketable debt securities	499.5	—	(0.5)	499.0	474.6	0.4	(0.1)	474.9
Corporate equity securities	69.4	167.1	(5.6)	230.9	51.4	144.4	—	195.8
Total marketable securities	$ 568.9	$ 167.1	$ (6.1)	$ 729.9	$ 526.0	$ 144.8	$ (0.1)	$ 670.7

Available-for-sale debt securities were classified on our consolidated balance sheets at fair value as follows:

	December 31,	
	2021	2020
	(in millions)	
Cash and cash equivalents	$ 3,478.1	$ 3,141.1
Marketable securities	499.0	474.9
Total	$ 3,977.1	$ 3,616.0

Available-for-sale debt securities by contractual maturity were as follows:

	December 31,	
	2021	2020
	(in millions)	
Matures within one year	$ 3,912.3	$ 3,526.2
Matures after one year through five years	64.8	89.8
Total	$ 3,977.1	$ 3,616.0

We have a limited number of available-for-sale debt securities in insignificant loss positions as of December 31, 2021, which we do not intend to sell and have concluded we will not be required to sell before recovery of the amortized costs for the investments at maturity. We did not record any charges for other-than-temporary declines in the fair value of available-for-sale debt securities or gross realized gains or losses in 2021, 2020 or 2019.

We record changes in the fair value of our investments in corporate equity securities to “Other income, net” in our consolidated statements of operations. During the three years ended December 31, 2021, our net unrealized gains on corporate equity securities held at the conclusion of each period were as follows:

	2021	2020	2019
	(in millions)		
Net unrealized gains	$ 17.1	$ 136.2	$ 143.2

During the years ended December 31, 2020 and 2019, we sold the common stock of publicly traded companies, which were primarily sales of our investment in CRISPR, resulting in the following:

	2020	2019
	(in millions)	
Proceeds received	$ 437.6	$ 94.9
Weighted-average cost basis	$ 103.3	$ 29.8

During the year ended December 31, 2021, we did not sell any common stock of publicly traded companies.

As of December 31, 2021, the carrying value of our equity investments without readily determinable fair values, which are recorded in “Other assets” on our consolidated balance sheets, was $85.8 million.

F. Accumulated Other Comprehensive Income (Loss)

The following table summarizes the changes in accumulated other comprehensive income (loss) by component:

	Foreign Currency Translation Adjustment	Unrealized Holding Gains (Losses), Net of Tax		Total
		On Available-For-Sale Debt Securities	On Foreign Currency Forward Contracts	
	(in millions)			
Balance as of December 31, 2018	$ (11.2)	$ (0.5)	$ 12.4	$ 0.7
Other comprehensive income before reclassifications	10.3	1.0	11.5	22.8
Amounts reclassified from accumulated other comprehensive income (loss)	—	—	(25.5)	(25.5)
Net current period other comprehensive income (loss)	10.3	1.0	(14.0)	(2.7)
Balance as of December 31, 2019	$ (0.9)	$ 0.5	$ (1.6)	$ (2.0)
Other comprehensive loss before reclassifications	(14.7)	(0.2)	(54.5)	(69.4)
Amounts reclassified from accumulated other comprehensive income (loss)	—	—	2.9	2.9
Net current period other comprehensive loss	(14.7)	(0.2)	(51.6)	(66.5)
Balance as of December 31, 2020	$ (15.6)	$ 0.3	$ (53.2)	$ (68.5)
Other comprehensive income (loss) before reclassifications	2.0	(0.8)	59.7	60.9
Amounts reclassified from accumulated other comprehensive income (loss)	—	—	23.5	23.5
Net current period other comprehensive income (loss)	2.0	(0.8)	83.2	84.4
Balance as of December 31, 2021	$ (13.6)	$ (0.5)	$ 30.0	$ 15.9

G. Hedging

Foreign currency forward contracts - Designated as hedging instruments

We maintain a hedging program intended to mitigate the effect of changes in foreign exchange rates for a portion of our forecasted product revenues denominated in certain foreign currencies. The program includes foreign currency forward contracts that are designated as cash flow hedges under U.S. GAAP having contractual durations from one to eighteen months. We recognize realized gains and losses for the effective portion of such contracts in “Product revenues, net” in our consolidated statements of operations in the same period that we recognize the product revenues that were impacted by the hedged foreign exchange rate changes.

We formally document the relationship between foreign currency forward contracts (hedging instruments) and forecasted product revenues (hedged items), as well as our risk management objective and strategy for undertaking various hedging activities, which includes matching all foreign currency forward contracts that are designated as cash flow hedges to forecasted transactions. We also formally assess, both at the hedge’s inception and on an ongoing basis, whether the foreign currency forward contracts are highly effective in offsetting changes in cash flows of hedged items on a prospective and retrospective basis. If we were to determine that a (i) foreign currency forward contract is not highly effective as a cash flow hedge, (ii) foreign currency forward contract has ceased to be a highly effective hedge or (iii) forecasted transaction is no longer probable of occurring, we would discontinue hedge accounting treatment prospectively. We measure effectiveness based on the change in fair value of the forward contracts and the fair value of the hypothetical foreign currency forward contracts with terms that match the critical terms of the risk being hedged. As of December 31, 2021, all hedges were determined to be highly effective.

We consider the impact of our counterparties' credit risk on the fair value of the foreign currency forward contracts. As of December 31, 2021 and December 31, 2020, credit risk did not change the fair value of our foreign currency forward contracts.

The following table summarizes the notional amount in U.S. dollars of our outstanding foreign currency forward contracts designated as cash flow hedges under U.S. GAAP:

	As of December 31,	
	2021	2020
Foreign Currency	**(in millions)**	
Euro	$ 1,364.5	$ 745.1
British pound sterling	287.7	160.4
Australian dollar	96.3	99.9
Canadian dollar	89.9	86.5
Swiss Franc	54.1	—
Total foreign currency forward contracts	$ 1,892.5	$ 1,091.9

Foreign currency forward contracts - Not designated as hedging instruments

We also enter into foreign currency forward contracts with contractual maturities of less than one month, which are designed to mitigate the effect of changes in foreign exchange rates on monetary assets and liabilities, including intercompany balances. These contracts are not designated as hedging instruments under U.S. GAAP. We recognize realized gains and losses for such contracts in "Other income, net" in our consolidated statements of operations each period. As of December 31, 2021, the notional amount of our outstanding foreign currency forward contracts where hedge accounting under U.S. GAAP is not applied was $580.7 million.

During the three years ended December 31, 2021, we recognized the following related to foreign currency forward contracts in our consolidated statements of operations:

	December 31,		
	2021	2020	2019
	(in millions)		
Designated as hedging instruments - Reclassified from AOCI			
Product revenues, net	$ (30.0)	$ (3.7)	$ 32.5
Not designated as hedging instruments			
Other income, net	$ (18.6)	$ 22.1	$ (4.8)
Total reported in the Consolidated Statement of Operations			
Product revenues, net	$ 7,573.4	$ 6,202.8	$ 4,160.7
Other income, net	$ 4.9	$ 296.6	$ 192.2

The following table summarizes the fair value of our outstanding foreign currency forward contracts designated as cash flow hedges under U.S. GAAP included on our consolidated balance sheets:

As of December 31, 2021			
Assets		**Liabilities**	
Classification	**Fair Value**	**Classification**	**Fair Value**
	(in millions)		
Prepaid expenses and other current assets	$ 44.5	Other current liabilities	$ (5.6)
Other assets	2.0	Other long-term liabilities	(2.7)
Total assets	$ 46.5	Total liabilities	$ (8.3)

As of December 31, 2020			
Assets		**Liabilities**	
Classification	**Fair Value**	**Classification**	**Fair Value**
	(in millions)		
Prepaid expenses and other current assets	$ —	Other current liabilities	$ (59.2)
Other assets	—	Other long-term liabilities	(4.3)
Total assets	$ —	Total liabilities	$ (63.5)

As of December 31, 2021, we expect the amounts that are related to foreign exchange forward contracts designated as cash flow hedges under U.S. GAAP recorded in “Prepaid expenses and other current assets” and “Other current liabilities” to be reclassified to earnings within twelve months.

As discussed in Note A, “Note A, “Nature of Business and Accounting Policies,” we present the fair value of our foreign currency forward contracts on a gross basis within our consolidated balance sheets. The following table summarizes the potential effect of offsetting derivatives by type of financial instrument designated as cash flow hedges under U.S. GAAP on our consolidated balance sheets:

	As of December 31, 2021				
	Gross Amounts Recognized	**Gross Amounts Offset**	**Gross Amounts Presented**	**Gross Amounts Not Offset**	**Legal Offset**
Foreign currency forward contracts			**(in millions)**		
Total assets	$ 46.5	$ —	$ 46.5	$ (8.3)	$ 38.2
Total liabilities	(8.3)	—	(8.3)	8.3	—

	As of December 31, 2020				
	Gross Amounts Recognized	**Gross Amounts Offset**	**Gross Amounts Presented**	**Gross Amounts Not Offset**	**Legal Offset**
Foreign currency forward contracts			**(in millions)**		
Total assets	$ —	$ —	$ —	$ —	$ —
Total liabilities	(63.5)	—	(63.5)	—	(63.5)

H. Inventories

Inventories consisted of the following:

	As of December 31,	
	2021	2020
	(in millions)	
Raw materials	$ 42.4	$ 46.2
Work-in-process	224.0	161.3
Finished goods	86.7	73.3
Total	$ 353.1	$ 280.8

I. Property and Equipment

Property and equipment, net consisted of the following:

	As of December 31,	
	2021	2020
	(in millions)	
Buildings and improvements	$ 892.5	$ 876.1
Furniture and equipment	407.3	346.7
Leasehold improvements	363.5	234.6
Computers and software	293.7	258.6
Land	33.1	33.1
Total property and equipment, gross	1,990.1	1,749.1
Less: accumulated depreciation	(896.0)	(790.6)
Total property and equipment, net	$ 1,094.1	$ 958.5

We recorded depreciation expense of $125.6 million, $109.5 million and $106.9 million in 2021, 2020 and 2019, respectively, which includes our finance lease amortization.

J. Intangible Assets and Goodwill

Intangible Assets

As of December 31, 2021 and 2020, we had $400.0 million of in-process research and development intangible assets classified as “Intangible assets” on our consolidated balance sheets. In 2019, we recorded $387.0 million and $13.0 million of in-process research and development intangible assets related to our acquisitions of Semma Therapeutics, Inc. (“Semma”) and Exonics, respectively.

Goodwill

As of December 31, 2021 and 2020, goodwill of $1.0 billion was recorded on our consolidated balance sheets. During 2019, we recorded goodwill of $554.6 million and $397.1 million related to our acquisitions of Semma and Exonics, respectively.

K. Additional Balance Sheet Detail

Prepaid expenses and other current assets consisted of the following:

	As of December 31,	
	2021	2020
	(in millions)	
Tax related prepaid and receivables	$ 358.6	$ 228.6
Other	187.2	79.7
Total	$ 545.8	$ 308.3

Accrued expenses consisted of the following:

	As of December 31,	
	2021	2020
	(in millions)	
Product revenue accruals	$ 847.4	$ 781.9
Payroll and benefits	191.3	169.4
Research, development and commercial contract costs	171.6	136.7
Royalty payable	200.4	165.4
Tax related accruals	211.3	104.2
Other	56.6	47.4
Total	$ 1,678.6	$ 1,405.0

Other current liabilities consisted of the following:

	As of December 31,	
	2021	2020
	(in millions)	
Contract liabilities	$ 171.7	$ 191.5
Finance lease liabilities	46.9	42.4
Fair value of cash flow hedges	5.6	59.2
Other	44.2	24.3
Total	$ 268.4	$ 317.4

The cash, cash equivalents and restricted cash balances at the beginning and ending of each period presented in our consolidated statements of cash flows consisted of the following:

	As of December 31,			
	2021	2020	2019	2018
	(in millions)			
Cash and cash equivalents	$ 6,795.0	$ 5,988.2	$ 3,109.3	$ 2,650.1
Prepaid expenses and other current assets	5.1	0.7	8.0	4.9
Other assets	—	—	3.4	3.3
Cash, cash equivalents and restricted cash per consolidated statement of cash flows	$ 6,800.1	$ 5,988.9	$ 3,120.7	$ 2,658.3

Our restricted cash, if any, is included in “Prepaid expenses and other current assets” and “Other assets” on our consolidated balance sheets.

L. Leases

Finance Leases

Our finance lease assets and liabilities primarily relate to our corporate headquarters in Boston and research site in San Diego (the “Buildings”). These Buildings are classified as finance leases because the present value of the sum of the lease payments associated with the Buildings exceeds substantially all of the fair value of the Buildings. We also have outstanding finance leases for equipment and land.

Corporate Headquarters

In 2011, we entered into two lease agreements, pursuant to which we lease approximately 1.1 million square feet of office and laboratory space in two buildings in Boston, Massachusetts for a term of 15 years. Base rent payments commenced in December 2013 and will continue through December 2028. We utilize this initial period as our lease term. We have an option to extend the lease term for an additional ten years.

San Diego Lease

In 2015, we entered into a lease agreement pursuant to which we lease approximately 170,000 square feet of office and laboratory space in San Diego, California for a term of 16 years. Base rent payments commenced in the second quarter of 2019 and will continue through May 2034. We utilize this initial period as our lease term. We have an option to extend the lease term for up to two additional five-year terms.

Operating Leases

Our operating leases relate to our real estate leases that are not classified as finance leases.

Innovation Square Lease

In 2019, we entered into an agreement to lease approximately 269,000 square feet of office and laboratory space near our corporate headquarters in Boston, Massachusetts. The lease agreement includes an initial term of 15 years plus a period to install leasehold improvements, with an option to extend the lease term for up to two additional ten-year periods. Base rent payments commenced in 2021. We have utilized the initial period, which commenced in the third quarter of 2020 upon occupation of the building, as our lease term.

Please refer to our accounting policy, *Leases*, in Note A, “Nature of Business and Accounting Policies,” for further information on the accounting treatment for our finance and operating leases.

Aggregate Lease Information

The components of lease cost recorded in our consolidated statement of operations were as follows:

	2021	2020	2019
		(in millions)	
Operating lease cost	$ 33.9	$ 23.1	$ 12.0
Finance lease cost			
Amortization of leased assets	51.9	51.2	49.8
Interest on lease liabilities	47.4	50.2	52.8
Variable lease cost	33.6	30.8	28.0
Sublease income	(0.4)	(4.0)	(6.4)
Net lease cost	$ 166.4	$ 151.3	$ 136.2

Our variable lease cost during 2021, 2020 and 2019 primarily related to operating expenses, taxes and insurance associated with our finance leases.

Our leases are included on our consolidated balance sheets as follows:

	As of December 31,	
	2021	2020
	(in millions)	
Finance leases		
Property and equipment, net	$ 400.1	$ 431.2
Total finance lease assets	$ 400.1	$ 431.2
Other current liabilities	$ 46.9	$ 42.5
Long-term finance lease liabilities	509.8	539.0
Total finance lease liabilities	$ 556.7	$ 581.5
Operating leases		
Operating lease assets	$ 330.3	$ 325.6
Total operating lease assets	$ 330.3	$ 325.6
Other current liabilities	$ 33.3	$ 10.5
Long-term operating lease liabilities	377.4	350.5
Total operating lease liabilities	$ 410.7	$ 361.0

Maturities of our finance and operating lease liabilities as of December 31, 2021 were as follows:

Year	Finance Leases	Operating Leases	Total
		(in millions)	
2022	$ 87.9	$ 41.9	$ 129.8
2023	93.2	42.0	135.2
2024	97.6	38.6	136.2
2025	95.9	35.7	131.6
2026	94.2	33.7	127.9
Thereafter	327.4	290.3	617.7
Total lease payments	796.2	482.2	1,278.4
Less: tenant allowance	—	(6.5)	(6.5)
Less: amount representing interest	(239.5)	(65.0)	(304.5)
Present value of lease liabilities	$ 556.7	$ 410.7	$ 967.4

The weighted-average remaining lease terms and discount rates related to our leases were as follows:

	As of December 31,	
	2021	2020
Weighted-average remaining lease term (in years)		
Finance leases	10.73	11.58
Operating leases	12.81	14.10
Weighted-average discount rate		
Finance leases	8.11 %	8.36 %
Operating leases	2.19 %	2.28 %

Supplemental cash flow information related to our leases was as follows:

	2021	2020	2019
		(in millions)	
Cash paid for amounts included in the measurement of lease liabilities			
Operating cash flows from operating leases	$ 21.5	$ 16.3	$ 10.7
Operating cash flows from finance leases	$ 46.2	$ 48.9	$ 50.5
Financing cash flows from finance leases	$ 47.0	$ 42.3	$ 39.2
Right-of-use assets obtained in exchange for lease obligations			
Operating leases	$ 36.3	$ 293.6	$ 34.6
Finance leases	$ —	$ 33.1	$ —

M. Common Stock, Preferred Stock and Equity Plans

Common Stock and Preferred Stock

We are authorized to issue 500.0 million shares of common stock. Holders of common stock are entitled to one vote per share. Holders of common stock are entitled to receive dividends, if and when declared by our Board of Directors, and to share ratably in our assets legally available for distribution to our shareholders in the event of liquidation. Holders of common stock have no preemptive, subscription, redemption or conversion rights. The holders of common stock do not have cumulative voting rights.

We are authorized to issue 1.0 million shares of preferred stock in one or more series and to fix the powers, designations, preferences and relative participating, option or other rights thereof, including dividend rights, conversion rights, voting rights, redemption terms, liquidation preferences and the number of shares constituting any series, without any further vote or action by our shareholders. As of December 31, 2021 and 2020, we had no shares of preferred stock issued or outstanding.

Share Repurchase Programs

In 2018, our Board of Directors approved a share repurchase program (the "2018 Share Repurchase Program"), pursuant to which we repurchased $500.0 million of our common stock in 2018 and 2019. During the year ended December 31, 2019, we repurchased 0.8 million shares of our common stock under the 2018 Share Repurchase Program for an aggregate of $150.0 million.

In July 2019, our Board of Directors approved a second share repurchase program (the "2019 Share Repurchase Program"), pursuant to which we repurchased $500.0 million of our common stock in 2019 and 2020. During the years ended December 31, 2020 and 2019, we repurchased 2.1 million and 0.2 million shares, respectively, of our common stock under the 2019 Share Repurchase Program for an aggregate of $464.0 million and $36.0 million, respectively.

In November 2020, our Board of Directors approved a third share repurchase program (the "2020 Share Repurchase Program"), pursuant to which we repurchased $500.0 million of our common stock in 2020 and 2021. During the years ended December 31, 2021 and 2020, we repurchased 2.0 million and 0.3 million shares, respectively, of our common stock under the 2020 Share Repurchase Program for an aggregate of $424.9 million and $75.1 million, respectively.

In June 2021, our Board of Directors approved a fourth share repurchase program (the "2021 Share Repurchase Program"), pursuant to which we are authorized to repurchase up to $1.5 billion of our common stock by December 31, 2022. During the year ended December 31, 2021, we repurchased 5.3 million shares of our common stock under the 2021 Share Repurchase Program for an aggregate of $1.0 billion. We expect to fund further repurchases of our common stock through a combination of cash on hand and cash generated by operations. As of December 31, 2021, $499.7 million remained authorized for repurchases of common stock under the 2021 Share Repurchase Program.

Repurchases of our common stock are recorded as reductions to "Common stock" and "Additional paid-in capital."

Stock and Option Plans

The purpose of each of our stock and option plans is to attract, retain and motivate our employees, consultants and directors. Awards granted under these plans can be nonstatutory stock options ("NSOs"), incentive stock options ("ISOs"), restricted stock units ("RSUs") including performance-based RSUs ("PSUs"), restricted stock ("RSs"), or other equity-based awards, as specified in the individual plans.

Shares issued under all of our plans are funded through the issuance of new shares. The following table contains information about our equity plans:

Title of Plan	Group Eligible	Type of Award Granted	As of December 31, 2021	
			Awards Outstanding	Additional Awards Authorized for Grant
			(in thousands)	
2013 Stock and Option Plan	Employees, Non-employee Directors and Consultants	NSO, RS, RSU and PSU	7,306	9,558
2006 Stock and Option Plan	Employees, Non-employee Directors and Consultants	NSO, RS and RSU	292	—
		Total	7,598	9,558

All options granted under our 2013 Stock and Option Plan ("2013 Plan") and 2006 Stock and Option Plan ("2006 Plan") were granted with an exercise price equal to the fair value of the underlying common stock on the date of grant. As of December 31, 2021, we are only authorized to make new equity awards under our 2013 Plan. Under the 2013 Plan, no stock options can be awarded with an exercise price less than the fair market value on the date of grant. In 2019, our shareholders approved an increase in the number of shares authorized for issuance pursuant to the 2013 Stock and Option Plan of 5.0 million shares.

During the three years ended December 31, 2021, grants to current employees and directors primarily had a grant date that was the same as the date the award was approved by our Board of Directors. During the three years ended December 31, 2021, for grants to new employees and directors, the date of grant for awards was the employee's first day of employment or the date the director was elected to our Board of Directors. All options awarded under our stock and option plans expire not more than 10 years from the grant date.

Stock Options

The following table summarizes information related to the outstanding and exercisable options during the year ended December 31, 2021:

	Stock Options	Weighted-average Exercise Price	Weighted-average Remaining Contractual Life	Aggregate Intrinsic Value
	(in thousands)	(per share)	(in years)	(in millions)
Outstanding at December 31, 2020	4,238	$ 140.47		
Granted	27	$ 217.20		
Exercised	(518)	$ 125.78		
Forfeited	(136)	$ 177.28		
Expired	—	$ —		
Outstanding at December 31, 2021	3,611	$ 141.76	5.42	$ 288.6
Exercisable at December 31, 2021	3,149	$ 136.13	5.19	$ 269.6

The aggregate intrinsic value in the table above represents the total pre-tax amount, net of exercise price, that would have been received by option holders if all option holders had exercised all options with an exercise price lower than the market price on the last business day of 2021, which was $221.27 based on the average of the high and low price of our common stock on that date.

The total intrinsic value (the amount by which the fair market value exceeded the exercise price) of stock options exercised during 2021, 2020 and 2019 was $43.0 million, $255.0 million and $325.9 million, respectively. The total cash we received as a result of employee stock option exercises during 2021, 2020 and 2019 was $64.2 million, $228.2 million and $317.8 million, respectively.

The following table summarizes information about stock options outstanding and exercisable at December 31, 2021:

	Options Outstanding			Options Exercisable	
Range of Exercise Prices	Number Outstanding	Weighted-average Remaining Contractual Life	Weighted-average Exercise Price	Number Exercisable	Weighted-average Exercise Price
	(in thousands)	(in years)	(per share)	(in thousands)	(per share)
$36.28–$100.00	1,085	3.70	$ 82.14	1,085	$ 82.14
$100.01–$150.00	362	3.56	$ 123.15	362	$ 123.15
$150.01–$200.00	2,114	6.53	$ 173.03	1,652	$ 171.04
$200.01–$286.27	50	8.92	$ 248.51	50	$ 248.51
Total	3,611	5.42	$ 141.76	3,149	$ 136.13

Restricted Stock Units (excluding PSUs) and Restricted Stock

The following table summarizes our restricted stock unit activity during the year ended December 31, 2021:

	Restricted Stock Units (excluding PSUs)	
	Number of Shares	Weighted-average Grant-date Fair Value
	(in thousands)	(per share)
Unvested at December 31, 2020	2,722	$ 206.99
Granted	1,927	$ 208.48
Vested	(1,331)	$ 193.29
Cancelled	(409)	$ 214.68
Unvested at December 31, 2021	2,909	$ 213.17

The total fair value of restricted stock units that vested during 2021, 2020 and 2019 (measured on the date of vesting) was $281.1 million, $370.3 million and $178.2 million, respectively. The total fair value of restricted stock that vested during 2020 and 2019 (measured on the date of vesting) was $21.4 million and $70.7 million, respectively. We have not granted any restricted stock since 2016, therefore, we did not have any restricted stock vest in 2021.

Performance-based RSUs (PSUs)

The potential range of shares issuable pursuant to our PSU awards range from 0% to 200% of the target shares based on financial and non-financial measures. Fifty percent of PSUs that could be earned have a one-year performance period with the amount actually earned dependent upon our financial performance and with vesting of the earned shares in three equal installments over a three-year period. The remaining 50% of PSUs that could be earned have a three-year performance period with the amount actually earned dependent upon the achievement of multiple clinical development milestones and with the earned shares cliff vesting at the end of the three-year performance period.

The following table summarizes our PSU activity during the year ended December 31, 2021:

	Performance-Based RSU	
	Number of Units	Weighted-average Grant-date Fair Value
	(in thousands)	(per share)
Unvested at December 31, 2020 (1)	656	$ 202.06
Granted (2)	954	$ 212.44
Vested	(431)	$ 183.94
Cancelled	(101)	$ 214.72
Unvested at December 31, 2021	1,078	$ 215.85

(1) “Unvested” represents our PSUs at target to the extent performance has not been certified plus the actual number of shares that continue to be subject to service conditions for which the performance has been achieved and certified.

(2) “Granted” represents (i) the target number of shares issuable for grants during 2021 and (ii) any change in the number of shares issuable pursuant to outstanding PSUs based on performance certification during 2021.

The total fair value of PSUs that vested during 2021, 2020 and 2019 (measured on the date of vesting) was $92.2 million, $138.5 million and $73.3 million, respectively.

Employee Stock Purchase Plan

We have an employee stock purchase plan (the “ESPP”). The ESPP permits eligible employees to enroll in a twelve-month offering period comprising two six-month purchase periods. Participants may purchase shares of our common stock, through payroll deductions, at a price equal to 85% of the fair market value of the common stock on the first day of the applicable twelve-month offering period, or the last day of the applicable six-month purchase period, whichever is lower. Purchase dates under the ESPP occur on or about May 14 and November 14 of each year. As of December 31, 2021, there were 1.8 million shares of common stock authorized for issuance pursuant to the ESPP.

In 2021, the following shares were issued to employees under the ESPP:

	Year Ended December 31, 2021
Number of shares (in thousands)	219
Average price paid per share	$ 171.57

Employee Benefits

We have a 401(k) retirement plan (the “Vertex 401(k) Plan”) in which substantially all of our permanent U.S. employees are eligible to participate. Participants may contribute up to 60% of their annual compensation to the Vertex 401(k) Plan, subject to statutory limitations. We may declare discretionary matching contributions to the Vertex 401(k) Plan. We pay matching contributions in the form of cash. For the years ended December 31, 2021, 2020 and 2019, we contributed approximately $21.8 million, $19.2 million and $15.8 million to the plan, respectively.

N. Stock-based Compensation Expense

We recognize share-based payments to employees as compensation expense using the fair value method. The fair value of stock options and shares purchased pursuant to the ESPP is calculated using the Black-Scholes option pricing model. The fair value of restricted stock units, including PSUs, is based on the intrinsic value on the date of grant. Stock-based compensation, measured at the grant date based on the fair value of the award, is typically recognized as expense ratably over the requisite service period.

The effect of stock-based compensation expense during the three years ended December 31, 2021 was as follows:

	2021	2020	2019
		(in millions)	
Stock-based compensation expense by line item:			
Cost of sales	$ 6.3	$ 5.6	$ 5.6
Research and development expenses	268.3	262.7	224.6
Selling, general and administrative expenses	166.8	161.2	130.3
Total stock-based compensation expense included in costs and expenses	441.4	429.5	360.5
Income tax effect	(82.9)	(147.0)	(124.2)
Total stock-based compensation included in costs and expenses, net of tax	$ 358.5	$ 282.5	$ 236.3

The stock-based compensation expense by type of award during the three years ended December 31, 2021 was as follows:

	2021	2020	2019
		(in millions)	
Stock-based compensation expense by type of award:			
Restricted stock units (including PSUs)	$ 384.3	$ 360.4	$ 254.3
Stock options	36.8	59.7	96.7
ESPP share issuances	24.4	13.0	11.2
Stock-based compensation expense related to inventories	(4.1)	(3.6)	(1.7)
Total stock-based compensation expense included in costs and expenses	$ 441.4	$ 429.5	$ 360.5

We capitalize a portion of our stock-based compensation expense to inventories, all of which is attributable to employees who support the manufacturing of our products.

The following table sets forth our unrecognized stock-based compensation expense as of December 31, 2021, by type of award and the weighted-average period over which that expense is expected to be recognized:

	As of December 31, 2021	
	Unrecognized Expense	Weighted-average Recognition Period
	(in millions)	(in years)
Type of award:		
Restricted stock units (including PSUs)	$ 423.3	1.91
Stock options	19.1	1.09
ESPP share issuances	12.6	0.54
Total unrecognized stock-based compensation expense	$ 455.0	

Stock Options

In each of the three years ended December 31, 2021, we issued stock options to our non-employee directors. In 2019, we issued stock options with service conditions, which were generally the vesting periods of the awards, to our employees. We use the Black-Scholes option pricing model to estimate the fair value of stock options at the grant date. The Black-Scholes option pricing model uses the option exercise price as well as estimates and assumptions related to the expected price volatility of our stock, the rate of return on risk-free investments, the expected period during which the options will be outstanding, and the expected dividend yield for our stock to estimate the fair value of a stock option on the grant date. The

options granted during 2021, 2020 and 2019 had a weighted-average grant-date fair value per share of $65.94, $88.37 and $61.32, respectively.

The fair value of each option granted during 2021, 2020 and 2019 was estimated on the date of grant using the Black-Scholes option pricing model with the following weighted-average assumptions:

	2021	2020	2019
Stock options granted	27,302	22,636	1,520,743
Expected stock price volatility	35.03%	35.87%	36.99%
Risk-free interest rate	0.86%	0.43%	2.32%
Expected term of options (in years)	4.50	4.67	4.27
Expected annual dividends	—	—	—

The weighted-average valuation assumptions were determined as follows:

- *Expected stock price volatility:* Expected stock price volatility is calculated using the trailing one-month average of daily implied volatilities prior to the grant date. Implied volatility is based on options to purchase our stock with remaining terms of greater than one year that are regularly traded in the market.
- *Risk-free interest rate:* We base the risk-free interest rate on the interest rate payable on U.S. Treasury securities in effect at the time of grant for a period that is commensurate with the assumed expected option term.
- *Expected term of options:* The expected term of options represents the period of time options are expected to be outstanding. We use historical data to estimate employee exercise and post-vest termination behavior. We believe that all groups of employees exhibit similar exercise and post-vest termination behavior and therefore do not stratify employees into multiple groups in determining the expected term of options.
- *Expected annual dividends:* The estimate for annual dividends is $0.00 because we have not historically paid, and do not intend for the foreseeable future to pay, a dividend.

Restricted Stock Units and Performance-based Restricted Stock Units

We award restricted stock units with service conditions, which are generally the vesting periods of the awards.

We grant PSUs to certain members of senior management. Half of the PSUs contain financial goals as the performance metric and the other half contain non-financial goals. A target number of shares is established for each award; however, the actual number of shares that are issued when an award vests may range from zero to 200% of the target amount depending upon the level of achievement of the applicable performance metric. The financial-based PSUs vest in three equal installments over a three-year period and are expensed ratably over that same period based upon an assessment of the likely level of achievement. The non-financial based PSUs cliff vest at the end of the three-year performance period and are expensed on a straight-line basis over that same period based upon an assessment of the likely level of achievement.

Employee Stock Purchase Plan

The weighted-average fair value of each purchase right granted during 2021, 2020 and 2019 was $51.71, $65.88 and $47.79, respectively. The following table reflects the weighted-average assumptions used in the Black-Scholes option pricing model for 2021, 2020 and 2019:

	2021	2020	2019
Expected stock price volatility	34.06%	37.70%	33.43%
Risk-free interest rate	0.05%	0.11%	2.08%
Expected term (in years)	0.69	0.71	0.74
Expected annual dividends	—	—	—

The weighted-average assumptions used in our Black-Scholes option pricing model were determined utilizing calculations similar to those described under *Stock Options* above.

O. Income Taxes

We are subject to U.S. federal, state, and foreign income taxes. The components of income before provision for income taxes during the three years ended December 31, 2021, consisted of the following:

	2021	2020	2019
		(in millions)	
United States	$ 2,030.7	$ 2,885.4	$ 1,263.4
Foreign	699.7	231.5	131.5
Income before provision for income taxes	$ 2,730.4	$ 3,116.9	$ 1,394.9

The components of the provision for income taxes during the three years ended December 31, 2021, consisted of the following:

	2021	2020	2019
		(in millions)	
Current taxes:			
Federal	$ 374.9	$ 71.4	$ —
Foreign	141.5	37.6	37.2
State	26.5	18.9	13.5
Total current taxes	542.9	127.9	50.7
Deferred taxes:			
Federal	(36.9)	510.2	184.3
Foreign	(98.4)	(239.6)	(24.8)
State	(19.3)	6.7	7.9
Total deferred taxes	(154.6)	277.3	167.4
Provision for income taxes	$ 388.3	$ 405.2	$ 218.1

A reconciliation between the U.S. federal statutory rate of 21% and our effective tax rate is as follows:

	2021	2020	2019
Federal statutory tax rate	21.0 %	21.0 %	21.0 %
State taxes, net of federal benefit	0.8 %	0.6 %	0.6 %
Foreign income tax rate differential	(0.3)%	0.2 %	0.4 %
Tax credits	(6.4)%	(1.8)%	(4.3)%
Tax rate change	(3.5)%	(1.2)%	— %
Stock compensation (benefit), shortfalls and cancellations	0.0 %	(2.3)%	(4.0)%
Long-term intercompany receivable write-off	— %	(1.7)%	— %
Uncertain tax positions	2.0 %	1.3 %	1.0 %
Inter-entity transfer of intellectual property rights	— %	(6.7)%	— %
U.S. tax on foreign earnings, net of credits	0.7 %	2.7 %	— %
Other	(0.1)%	0.9 %	0.9 %
Effective tax rate	14.2 %	13.0 %	15.6 %

Our 14% effective tax rate for 2021 was lower than the U.S. statutory rate primarily due to discrete tax benefits of (i) $94.8 million associated with an increase in the United Kingdom's ("U.K.") corporate tax rate from 19% to 25%, which was enacted in June 2021 and will become effective in April 2023, and (ii) $44.1 million resulting from an R&D tax credit study that we completed in 2021.

Our 13% effective tax rate for 2020 was lower than the U.S. statutory rate primarily due to (i) a discrete tax benefit of $209.0 million associated with an intra-entity transfer of intellectual property rights to our U.K. entity, (ii) a discrete tax benefit associated with the write-off of a long-term intercompany receivable, (iii) a discrete tax benefit associated with an increase in the U.K.'s corporate tax rate from 17% to 19%, which was enacted and became effective in July 2020, and (iv) excess tax benefits related to stock-based compensation. The impact of these items was partially offset by U.S. income tax on foreign earnings.

Our 16% effective tax rate for 2019 was lower than the U.S. statutory rate primarily due to excess tax benefits related to stock-based compensation and research and development tax credits.

Deferred tax assets and liabilities are determined based on the difference between financial statement and tax bases using enacted tax rates in effect for the year in which the differences are expected to reverse. The components of the deferred taxes were as follows:

	As of December 31,	
	2021	2020
	(in millions)	
Deferred tax assets:		
Net operating loss	$ 106.6	$ 140.6
Tax credit carryforwards	202.4	406.1
Intangible assets	802.8	507.5
Stock-based compensation	94.6	89.2
Accrued expenses	48.6	47.3
Finance lease liabilities	103.4	118.7
Operating lease assets	81.1	65.0
Other	41.7	22.1
Gross deferred tax assets	1,481.2	1,396.5
Valuation allowance	(220.4)	(213.8)
Total deferred tax assets	1,260.8	1,182.7
Deferred tax liabilities:		
Property and equipment	(118.2)	(117.0)
Acquired intangibles	(87.0)	(87.0)
Operating lease liabilities	(64.8)	(63.3)
Other	(56.3)	(32.6)
Total deferred tax liabilities	(326.3)	(299.9)
Net deferred tax assets	$ 934.5	$ 882.8

On a periodic basis, we reassess the valuation allowance on our deferred income tax assets, weighing positive and negative evidence to assess the recoverability of our deferred tax assets. As of December 31, 2021, we maintained a valuation allowance of $220.4 million related primarily to U.S. state tax attributes.

As of December 31, 2021, we had net operating loss (“NOL”) carryforwards of $29.8 million and tax credit carryforwards of $4.1 million, which are subject to annual utilization limitations for U.S. federal income tax purposes. As of December 31, 2021, we had NOL carryforwards of $616.3 million and tax credit carryforwards of $237.2 million for U.S. state income tax purposes. In 2030, $26.0 million of our U.S. federal NOLs will begin to expire, while the remaining portion may be carried forward indefinitely. The state NOL and tax credit carryforwards expire at various dates through 2041 and may be used to offset future state income tax liabilities. As of December 31, 2021, we had foreign NOL carryforwards of $292.5 million and foreign tax credit carryforwards of $22.2 million. The foreign NOL carryforwards may be carried forward indefinitely, with the exception of $44.3 million that will expire at various dates through 2040. The foreign tax credit carryforwards will begin to expire in 2024.

Unrecognized tax benefits during the three years ended December 31, 2021 were as follows:

	2021	2020	2019
		(in millions)	
Balance at beginning of the period	$ 86.6	$ 33.9	$ 19.5
Increases related to current period tax positions	42.0	26.7	14.5
Increases related to prior period tax positions	19.9	26.7	0.6
Decreases related to prior period tax positions	—	—	(0.2)
Settlement with tax authorities	—	—	(0.5)
Statute of limitations expiration	(1.3)	(0.7)	—
Balance at end of period	$ 147.2	$ 86.6	$ 33.9

As of December 31, 2021, we have classified $14.4 million and $132.8 million of our unrecognized tax benefits as credits to “Deferred tax assets” and “Accrued expenses,” respectively, on our consolidated balance sheet.

We have reviewed the tax positions taken, or to be taken, in our tax returns for all tax years currently open to examination by a taxing authority. Unrecognized tax benefits represent the aggregate tax effect of differences between tax return positions and the benefits recognized in our consolidated financial statements. As of December 31, 2021, 2020 and 2019, we had $129.5 million, $75.8 million and $33.9 million, respectively, of net unrecognized tax benefits, which would affect our tax rate if recognized. We do not expect that our unrecognized tax benefits will materially change within the next twelve months. We did not recognize any material interest or penalties related to uncertain tax positions during the three years ended December 31, 2021.

As of December 31, 2021, foreign earnings have been retained by our foreign subsidiaries for indefinite reinvestment. Upon repatriation of those earnings, in the form of dividends or otherwise, we could be subject to U.S. federal withholding taxes payable to various foreign countries and income taxes in certain states. We are permanently reinvested for book/tax basis differences. These permanently reinvested basis differences could reverse if we sell our foreign subsidiaries or various other events, none of which were considered probable as of December 31, 2021. The tax liabilities described above would not be material to our consolidated financial statements.

We file U.S. federal income tax returns and income tax returns in various state, local and foreign jurisdictions. We have various income tax audits ongoing at any time throughout the world. Except for jurisdictions where we have NOLs or tax credit carryforwards, we are no longer subject to any tax assessment from tax authorities for years prior to 2018.

P. Commitments and Contingencies

Revolving Credit Facilities

Vertex and certain of its subsidiaries have entered into two credit agreements (the “Credit Agreements”) with Bank of America, N.A., as administrative agent and the lenders referred to therein (the “Lenders”). The Credit Agreements were not drawn upon at closing and we have not drawn upon them to date. Amounts drawn pursuant to the Credit Agreements, if any, will be used for general corporate purposes. Any amounts borrowed under the Credit Agreements will bear interest, at our option, at either a base rate or a Eurocurrency rate, in each case plus an applicable margin based on our consolidated leverage ratio (the ratio of our total consolidated funded indebtedness to our consolidated EBITDA for the most recently completed four fiscal quarter period).

In September 2019, Vertex and certain of its subsidiaries entered into a $500.0 million unsecured revolving facility (the “2019 Credit Agreement”) with the Lenders, which matures on September 17, 2024. Under the 2019 Credit Agreement, the applicable margins on base rate loans range from 0.125% to 0.500% and the applicable margins on Eurocurrency loans range from 1.125% to 1.500%. The 2019 Credit Agreement provides a sublimit of $50.0 million for letters of credit.

In September 2020, Vertex and certain of its subsidiaries entered into a $2.0 billion unsecured revolving facility (the

"2020 Credit Agreement") with the Lenders, which matures on September 18, 2022. Under the 2020 Credit Agreement, the applicable margins on base rate loans range from 0.500% to 0.875% and the applicable margins on Eurocurrency loans range from 1.500% to 1.875%. The 2020 Credit Agreement does not support letters of credit.

Subject to satisfaction of certain conditions, we may request that the borrowing capacity for each of the Credit Agreements be increased by an additional $500.0 million. Any amounts borrowed pursuant to the Credit Agreements are guaranteed by certain of our existing and future domestic subsidiaries, subject to certain exceptions.

The Credit Agreements contain customary representations and warranties and affirmative and negative covenants, including financial covenants to maintain (x) subject to certain limited exceptions, a consolidated leverage ratio of 3.50 to 1.00, subject to an increase to 4.00 to 1.00 following a material acquisition and (y) a consolidated interest coverage ratio of 2.50 to 1.00, in each case measured on a quarterly basis. As of December 31, 2021, we were in compliance with the covenants described above. The Credit Agreements also contain customary events of default. In the case of a continuing event of default, the administrative agent would be entitled to exercise various remedies, including the acceleration of amounts due under outstanding loans.

Direct costs related to the Credit Agreements are recorded over the term of the Credit Agreements and were not material to our financial statements.

Guaranties and Indemnifications

As permitted under Massachusetts law, our Articles of Organization and By-laws provide that we will indemnify certain of our officers and directors for certain claims asserted against them in connection with their service as an officer or director. The maximum potential amount of future payments that we could be required to make under these indemnification provisions is unlimited. However, we have purchased directors' and officers' liability insurance policies that could reduce our monetary exposure and enable us to recover a portion of any future amounts paid. No indemnification claims currently are outstanding, and we believe the estimated fair value of these indemnification arrangements is minimal.

We customarily agree in the ordinary course of our business to indemnification provisions in agreements with clinical trial investigators and sites in our drug development programs, sponsored research agreements with academic and not-for-profit institutions, various comparable agreements involving parties performing services for us, and our real estate leases. We also customarily agree to certain indemnification provisions in our drug discovery, development and commercialization collaboration agreements. With respect to our clinical trials and sponsored research agreements, these indemnification provisions typically apply to any claim asserted against the investigator or the investigator's institution relating to personal injury or property damage, violations of law or certain breaches of our contractual obligations arising out of the research or clinical testing of our compounds or product candidates. With respect to lease agreements, the indemnification provisions typically apply to claims asserted against the landlord relating to personal injury or property damage caused by us, to violations of law by us or to certain breaches of our contractual obligations. The indemnification provisions appearing in our collaboration agreements are similar to those for the other agreements discussed above, but in addition provide some limited indemnification for our collaborator in the event of third-party claims alleging infringement of intellectual property rights. In each of the cases above, the indemnification obligation generally survives the termination of the agreement for some extended period, although we believe the obligation typically has the most relevance during the contract term and for a short period of time thereafter. The maximum potential amount of future payments that we could be required to make under these provisions is generally unlimited. We have purchased insurance policies covering personal injury, property damage and general liability that reduce our exposure for indemnification and would enable us in many cases to recover all or a portion of any future amounts paid. We have never paid any material amounts to defend lawsuits or settle claims related to these indemnification provisions. Accordingly, we believe the estimated fair value of these indemnification arrangements is minimal.

Other Contingencies

We have certain contingent liabilities that arise in the ordinary course of our business activities. We accrue a reserve for contingent liabilities when it is probable that future expenditures will be made and such expenditures can be reasonably estimated. Other than our contingent consideration liabilities discussed in Note D, "Fair Value Measurements," there were no material contingent liabilities accrued as of December 31, 2021 or 2020.

Q. Segment Information

Segment reporting is prepared on the same basis that our chief executive officer, who is our chief operating decision maker, manages the business, makes operating decisions and assesses performance. We operate in one segment, pharmaceuticals. Enterprise-wide disclosures about revenues, significant customers, and property and equipment, net by location are presented below.

Revenues by Product

Product revenues, net consisted of the following:

	2021	2020	2019
		(in millions)	
TRIKAFTA/KAFTRIO	$ 5,697.2	$ 3,863.8	$ 420.1
SYMDEKO/SYMKEVI	420.4	628.6	1,417.7
ORKAMBI	771.6	907.5	1,331.9
KALYDECO	684.2	802.9	991.0
Total product revenues, net	$ 7,573.4	$ 6,202.8	$ 4,160.7

Product Revenues by Geographic Location

Net product revenues are attributed to countries based on the location of the customer and consisted of the following:

	2021	2020	2019
		(in millions)	
United States	$ 5,287.3	$ 4,826.4	$ 3,060.3
Outside of the United States			
Europe	1,972.9	1,126.5	885.9
Other	313.2	249.9	214.5
Total product revenues outside of the United States	2,286.1	1,376.4	1,100.4
Total product revenues, net	$ 7,573.4	$ 6,202.8	$ 4,160.7

Significant Customers

Gross product revenues and accounts receivable from each of our customers who individually accounted for 10% or more of total gross product revenues and/or 10% or more of total accounts receivable consisted of the following:

	Percent of Total Gross Product Revenues			Percent of Accounts Receivable	
	Year Ended December 31,			As of December 31,	
	2021	2020	2019	2021	2020
McKesson Corporation	22 %	20 %	17 %	21 %	14 %
Accredo/Curascript	12 %	15 %	14 %	10 %	10 %
Walgreen Co.	10 %	14 %	15 %	<10 %	10 %
Lloyds Pharmacy*	<10%	<10%	<10%	15 %	19 %

*A wholly-owned subsidiary of McKesson Corporation in the U.K.

Long-lived Assets by Location

Long-lived assets by location consisted of the following:

	As of December 31,	
	2021	2020
	(in millions)	
United States	$ 1,348.1	$ 1,207.7
Outside of the United States		
United Kingdom	60.9	61.5
Other	15.4	14.9
Total long-lived assets outside of the United States	76.3	76.4
Total long-lived assets	$ 1,424.4	$ 1,284.1

EXHIBIT 10.24

AMENDMENT NO. 1 TO
EMPLOYMENT AGREEMENT

This AMENDMENT NO. 1 is made and entered into effective as of February 7, 2022 (the "Effective Date") to the employment agreement dated as of April 1, 2020 (the "Employment Agreement"), between Vertex Pharmaceuticals Incorporated (the "Company") and Jeffrey M. Leiden, MD., Ph.D. (the "Executive").

NOW, THEREFORE, in consideration of the mutual covenants set forth herein, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Company and Executive agree as follows:

1. That Section 2 of the Employment Agreement is hereby amended by deleting "March 31, 2023" and replacing it with "March 31, 2024".

2. That Section 3(d) of the Employment Agreement is hereby amended by deleting "2023" and replacing it with "2024".

3. That Section 4(c) of the Employment Agreement is hereby amended in its entirety by replacing it with the following:

"(c) Equity Awards. During the Term of this Agreement, and provided that the Executive has remained in continuous service with the Company through the applicable grant date, subject to the approval of the Board or the Compensation Committee thereof, the Executive will receive the following annual grants of equity awards (the "Annual Stock Awards"). Each Annual Stock Award will be made during the applicable time period set forth below. Fifty percent (50%) of each Annual Stock Award will be in the form of fully vested shares of Company common stock and fifty percent (50%) will be in the form of performance stock units and the Annual Stock Award will have an aggregate grant date value (with performance stock units valued based on target, and the number of shares or units granted, as applicable, determined by dividing such values by the fair market value of the Company's common stock) as follows:

(i) $9,000,000 for fiscal year 2020 (to be granted in the first calendar quarter of 2021) ("Year 1");

(ii) $8,500,000 for fiscal year 2021 (to be granted in the first calendar quarter of 2022) ("Year 2");

(iii) $6,500,000 for fiscal year 2022 (to be granted in the first calendar quarter of 2023) ("Year 3"); and

(iv) $6,500,000 for fiscal year 2023 (to be granted in the first calendar quarter of 2024) ("Year 4").

Both one-year and three-year performance criteria will apply to the performance stock units granted in Year 1, and one-year performance criteria will apply to the performance stock units granted in Year 2, Year 3 and Year 4. The terms and conditions applicable to each Annual Stock Award shall otherwise be as prescribed by the Compensation Committee, with each Annual Stock Award evidenced by an award agreement that is substantially similar to the form of award agreement used for such type of award for Company executives generally, except for such changes as are necessary or desirable to reflect the terms of the Executive's employment hereunder."

4. That Section 4(d) of the Employment Agreement is hereby amended adding a final sentence to such Section as follows:

   "In order to facilitate the Executive's receipt of benefits under the Employee Benefit Plans in 2022, 2023 and 2024, the Company will make a cash payment to executive of $65,000 in each of February 2022, February 2023 and February 2024."

5. Except as amended hereby and expressly provided herein, the Employment Agreement shall remain in full force and effect.

IN WITNESS WHEREOF, this Amendment No. 1 has been executed as a sealed instrument by the Company, by its duly authorized representative, and by the Executive, as of the date first above written.

THE COMPANY:

VERTEX PHARMACEUTICALS INCORPORATED

By: /s/ Bruce I. Sachs
Bruce I. Sachs
Lead Independent Director and Chairman of MDCC

THE EXECUTIVE:

/s/ Jeffrey M. Leiden
Jeffrey M. Leiden, M.D., Ph.D

EMPLOYMENT AGREEMENT

This Employment Agreement (this "Agreement") is made and entered into as of this 1st day of August, 2020, by and between Vertex Pharmaceuticals Incorporated, a Massachusetts corporation (together with its successors and assigns, the "Company"), and Nia Tatsis (the "Executive").

W IT N E S S E T H

WHEREAS, the Company and the Executive desire that the Executive be appointed and serve as an Executive Vice President of the Company as of the Effective Date; and

WHEREAS, the Company and the Executive desire to enter into this Agreement to set forth the terms of the Executive's continued employment with the Company;

NOW, THEREFORE, in consideration of the promises and mutual covenants contained herein and for other good and valuable consideration, the receipt of which mutually is acknowledged, the Company and the Executive (each individually a "Party", and together the "Parties") agree as follows:

1. DEFINITIONS.

"Accrued Benefits" shall mean (i) any Base Salary earned by the Executive but not then paid and (ii) any accrued and vested but then unpaid benefits under the Benefit Plans, in each case, through the date of termination of the Executive's employment.

"Base Salary" shall mean the Executive's base salary in accordance with Section 4 below.

"Benefit Plans" shall mean all employee welfare and pension benefit plans, programs and/or arrangements offered by the Company to its senior executives.

"Board" shall mean the Board of Directors of the Company.

"Cause" shall mean:

(i) the Executive is convicted of a crime involving moral turpitude;

(ii) the Executive's willful refusal or failure to follow a lawful directive or instruction of the Company's Board of Directors or the individual(s) to whom the Executive reports, provided that the Executive receives prior written notice of the directive(s) or instruction(s) that the Executive failed to follow, and provided further that the Company, in good faith, gives the Executive 30 days to correct such failure and further provided that if the Executive corrects the failure(s), any termination of the Executive's employment on account of such failure shall not be treated for purposes of this Agreement as a termination of employment for "Cause";

(iii) the Executive commits a material breach of the Company's insider trading policy or of any provision of this Agreement or the agreement between the Company and the Executive entitled "Employee Non-Disclosure, Non-Competition and Inventions Agreement" dated as of July 23, 2017 (the "Inventions Agreement"); or

(iv) the Executive commits a breach of the code of conduct or any other material policy of the Company or any of its affiliates that is damaging to the financial condition or reputation of the Company or any of its affiliates.

"Change of Control" shall have the meaning set forth in the Change of Control Agreement.

"Change of Control Agreement" shall mean the Change of Control letter agreement between the Company and the Executive of even date herewith.

"Code" shall mean the Internal Revenue Code of 1986, as amended.

"Common Stock" shall mean the common stock of the Company.

"Compensation Committee" shall mean the Management Development and Compensation Committee of the Board.

"Disability" or "Disabled" shall mean a disability as determined under the Company's long-term disability plan or program in effect at the time the disability first occurs, or if no such plan or program exists at the time of disability, then a "disability" as defined under Section 22(e)(3) of the Code.

"Effective Date" shall mean August 1, 2020.

"Good Reason" shall mean that, without the Executive's consent, one or more of the following events occurs:

(i) the Executive's duties are materially diminished to an extent that results in the Executive no longer being an "officer," as such term is defined in Rule 16a-1(f) promulgated under the Securities Exchange Act of 1934;

(ii) the Executive's Base Salary is decreased unless such reduction is part of an across-the-board proportionate reduction in the base salaries of the Company's senior management team; or

(iii) the office to which the Executive is assigned is relocated to a place 35 or more miles away and such relocation is not (A) at the Executive's request or (B) in connection with a change in location of the Company's principal executive offices;

provided that Good Reason shall not exist unless and until within 30 days after the event giving rise to Good Reason under either (i) or (ii) above has occurred, the Executive delivers a written termination notice to the Company stating that an event giving rise to Good Reason has occurred and identifying with reasonable detail the event that the Executive asserts constitutes Good Reason under either (i) or (ii) above and the Company fails or refuses to cure or eliminate the event giving rise to Good Reason on or within 30 days after receiving such notice and, with respect to the event giving rise to Good Reason under (iii) above, the Executive delivers a written termination notice to the Company within 30 days after the event giving rise to Good Reason occurs. To avoid doubt, the termination of the Executive's employment will become effective at the close of business on the thirtieth day after the Company receives the Executive's termination notice, unless, in the case of an event giving rise to Good Reason under either (i) or (ii) above, the Company cures or eliminates the event giving rise to Good Reason prior to such time.

"Severance Payment" shall mean an amount equal to (x) 100% of the sum of (A) the Base Salary in effect on the date of termination of the Executive's employment, plus (B) the full amount of the Target Bonus for the Executive for the year in which the Executive's employment is terminated, plus (y) any annual bonus earned by the Executive in respect of the year prior to the year in which the termination of the Executive's employment occurs, if not yet paid; provided, however, that if the Executive terminates the Executive's employment for Good Reason based on a reduction in Base Salary, then the Base Salary to be used in calculating the Severance Payment shall be the Base Salary in effect immediately prior to such reduction in Base Salary.

"Target Bonus" shall mean the target cash bonus for which the Executive is eligible on an annual basis, at a level consistent with the Executive's title and responsibilities, under the Company's bonus program then in effect and applicable to the Company's senior executives generally.

2. TERM OF EMPLOYMENT.

The Company hereby continues to employ the Executive, and the Executive hereby accepts such employment as of the Effective Date, continuing until termination in accordance with the terms of this Agreement. The period during which the Executive is employed hereunder is referred to in this Agreement as the "term of employment."

3. POSITION.

On the Effective Date, the Executive will be employed as one of the Company's Executive Vice Presidents.

4. BASE SALARY.

The Executive's annualized Base Salary as of the Effective Date will be $550,000, payable in accordance with the regular payroll practices of the Company. The Base Salary shall be reviewed no less frequently than annually, and any increases thereto (which shall thereafter be deemed the Executive's Base Salary) shall be solely within the discretion of the Board or the Compensation Committee.

5. ANNUAL BONUS.

During the term of employment, the Executive shall be eligible to participate in the Company's annual cash incentive compensation program applicable to the Company's senior executives generally, as any such programs are established and modified from time to time by the Board or the Compensation Committee in its sole discretion, and in accordance with the terms of such program, with a Target Bonus as determined by the Board or the Compensation Committee. The Target Bonus for fiscal year 2020 is 70% of Base Salary.

6. EQUITY COMPENSATION PROGRAMS.

During the term of employment, the Executive shall be eligible to participate in the Company's equity incentive compensation programs applicable to the Company's senior executives, as such programs may be established and modified from time to time by the Board or the Compensation Committee in its sole discretion. Nothing in this Agreement shall preclude the Company from amending or terminating any of its equity incentive compensation plans, programs or arrangements.

7. EMPLOYEE BENEFIT PROGRAMS.

During the term of employment, the Executive shall be entitled to participate in the Benefit Plans, as such Benefit Plans may be amended from time to time, to the same extent and on the same terms applicable to other senior executives. Nothing in this Agreement shall preclude the Company from amending or terminating any of the Benefit Plans.

8. VACATION.

During the term of employment, the Executive shall be entitled to at least 20 paid vacation days each calendar year in accordance with the Company's vacation policy then in effect.

9. TERMINATION OF EMPLOYMENT.

(a) **Termination in Connection with a Change of Control**. To the extent the Executive is entitled, in connection with the Executive's termination of employment, to severance or other benefits under the Change of Control Agreement, the Executive shall not be entitled to any benefits under this Section 9.

(b) **Termination by the Company for Cause; or Termination by the Executive without Good Reason.** If the Company terminates the Executive's employment for Cause, or if the Executive terminates the Executive's employment, other than for Good Reason, death or Disability, the term of employment shall end as of the date specified below, and the Executive shall be entitled to the Accrued Benefits. Any equity awards held by the Executive on the date of termination shall be governed by the applicable equity plan, any applicable grant agreements and any applicable Company securities trading policies. Termination by the Company for Cause shall be effective as of the date specified in the notice of termination provided by the Company to the Executive. Termination by the Executive other than for Good Reason, death or Disability shall be effective upon 60 days' prior written notice to the Company. Other than as set forth expressly in this Section 9(b), the Company shall have no obligation or liability to the Executive.

(c) **Termination by the Company Without Cause; or Termination by the Executive for Good Reason.** If the Executive's employment is terminated by the Company without Cause (other than due to death or Disability), or is terminated by the Executive for Good Reason (in accordance with the notice and cure provisions set forth in the definition of "Good Reason" above), the Executive shall be entitled to the Accrued Benefits. In addition, the Executive shall be entitled to the following:

(i) a lump sum cash payment to the Executive in an amount equal to the Severance Payment, payable within ten days after execution of the Release (defined below) and expiration, without revocation, of any applicable revocation periods under the Release, provided that if the 60-day period during which the Release is required to become effective and irrevocable begins in one calendar year and ends in another calendar year, the Severance Payment shall not be made before the first day of the second calendar year;

(ii) if COBRA coverage is elected by the Executive, the Company shall pay the cost of insurance continuation premiums on the Executive's behalf (whether or not covered by COBRA) to continue standard medical, dental and life insurance coverage for the Executive and the Executive's eligible dependents (or the cash equivalent of same in the event the Executive or the Executive's eligible dependents are ineligible for continued coverage), on a monthly basis, until the earlier of:

(A) the date 12 months after the date the Executive's employment is terminated; or

(B) the date, or dates, on which the Executive receives equivalent coverage and benefits under the plans, programs and/or arrangements of a subsequent employer (such coverage and benefits to be determined on a coverage-by-coverage or benefit-by-benefit basis).

Other than as set forth expressly in this Section 9(c), the Company shall have no obligation or liability to the Executive.

(d) **Conditions to Severance.** Any payments and benefits provided under this Section 9, other than the Accrued Benefits, shall be subject to and in exchange for a general release of all claims against the Company, its subsidiaries, and their officers, directors, agents and representatives (the "Release"), which is executed by the Executive (or the Executive's estate, as

applicable) and becomes enforceable and non-revocable within 60 days of the date of the Executive's termination of employment. Moreover, notwithstanding anything to the contrary in this Agreement, if at the time of the Executive's termination of employment, the Executive is a "specified employee" (as defined below), any payment of "nonqualified deferred compensation" (as defined under Section 409A of the Code, as amended, including the regulations thereunder ("Section 409A")) that is payable on a "separation from service" (as defined below) shall not commence until the first full business day that is six months and one day after the applicable separation from service (or, if earlier, the Executive's death) (the "Deferred Payment Date"); except (A) to the extent of amounts that do not constitute a deferral of compensation within the meaning of Treasury regulation Section 1.409A-1(b) (including without limitation by reason of the safe harbor set forth in Section 1.409A-1(b)(9)(iii), as determined by the Company in its reasonable discretion); (B) benefits that qualify as excepted welfare benefits pursuant to Treasury regulation Section 1.409A-1(a)(5); or (C) other amounts or benefits that are not subject to the requirements of Section 409A. Any payments that would otherwise have been made between the separation from service and the Deferred Payment Date, but for this paragraph, shall be made in a lump sum on the Deferred Payment Date. For purposes of this Agreement, to the extent required to ensure compliance with Section 409A of the Code, all references to "termination of employment" and correlative phrases shall be construed to require a "separation from service" (as defined in Section 1.409A-1(h) of the Treasury regulations, after giving effect to the presumptions contained therein), and the term "specified employee" means an individual determined by the Company to be a specified employee under Treasury regulation Section 1.409A-1(i).

10. ASSIGNABILITY; BINDING NATURE.

This Agreement shall be binding upon and inure to the benefit of the Parties and their respective successors, heirs (in the case of the Executive) and assigns. No rights or obligations of the Company under this Agreement may be assigned or transferred by the Company except that such rights or obligations may be assigned or transferred pursuant to a merger or consolidation in which the Company is not the continuing entity, or the sale or liquidation of all or substantially all of the assets of the Company; provided, however, that the assignee or transferee is the successor to all or substantially all of the assets of the Company and such assignee or transferee assumes the liabilities, obligations and duties of the Company, as contained in this Agreement, either contractually or as a matter of law.

11. REPRESENTATIONS.

The Company represents and warrants that it is fully authorized and empowered to enter into this Agreement, and that the performance of its obligations under this Agreement will not violate any agreement between it and any other person, firm or organization. The Executive represents and warrants that no agreement exists between the Executive and any other person, firm or organization that would be violated by the performance of the Executive's obligations under this Agreement.

12. INDEMNIFICATION; INSURANCE.

The Executive shall at all times be indemnified and eligible for advancement of expenses on the same basis as is provided for the Company's other executive officers and in accordance with the provisions of the Company's charter and by-laws then in effect. The Executive shall also be covered under all of the Company's policies of liability insurance maintained for the benefit of its directors and officers on the same basis as is provided for its other executive officers.

13. ENTIRE AGREEMENT; TERMINATION.

This Agreement, the agreements referenced herein and the Inventions Agreement previously entered into between the Executive and the Company contain the entire understanding

and agreement between the Parties concerning the subject matter hereof and supersedes as of the Effective Date all prior agreements, understandings, discussions, negotiations and undertakings, whether written or oral, between the Parties with respect thereto and supersedes and terminates as of the Effective Date the offer letter dated July 21, 2017. Subject to the terms of this Agreement, the Company shall be entitled to terminate the Executive's employment at any time, and the Executive may terminate the Executive's employment by the Company, at any time subject to the provisions of Section 9(b) of this Agreement, in each case by written notice provided in accordance with Section 20 of this Agreement.

14. AMENDMENT OR WAIVER.

No provision in this Agreement may be amended unless such amendment is agreed to in writing and signed by the Executive and an authorized officer of the Company provided that the Company may, without the Executive's consent, unilaterally adopt amendments that may be required so that this Agreement continues to comply with applicable law or regulations, including without limitation Section 409A. No waiver by either Party of any breach by the other Party of any condition or provision contained in this Agreement to be performed by such other Party shall be deemed a waiver of a similar or dissimilar condition or provision at the same or any prior or subsequent time. Any waiver must be in writing and signed by the Executive or an authorized officer of the Company, as the case may be.

15. SEVERABILITY.

If any provision or portion of this Agreement shall be determined to be invalid or unenforceable for any reason, in whole or in part, the remaining provisions of this Agreement shall be unaffected thereby and shall remain in full force and effect to the fullest extent permitted by law.

16. SURVIVORSHIP.

The respective rights and obligations of the Parties hereunder shall survive any termination of the Executive's employment to the extent necessary to the intended preservation of such rights and obligations.

17. BENEFICIARIES/REFERENCES.

The Executive shall be entitled, to the extent permitted under any applicable law, to select and change a beneficiary or beneficiaries to receive any compensation or benefit payable hereunder following the Executive's death by giving the Company written notice thereof. In the event of the Executive's death or a judicial determination of the Executive's incompetence, reference in this Agreement to the Executive shall be deemed, where appropriate, to refer to the Executive's beneficiary, estate or other legal representative.

18. GOVERNING LAW/JURISDICTION.

This Agreement shall be governed by and construed and interpreted in accordance with the laws of The Commonwealth of Massachusetts without reference to principles of conflict of laws.

19. RESOLUTION OF DISPUTES.

Any disputes arising under or in connection with this Agreement will, at the election of the Executive or the Company, be resolved by binding arbitration, to be held in Massachusetts in accordance with the Rules and Procedures of the American Arbitration Association. If arbitration is elected, the Executive and the Company shall mutually select the arbitrator. If the Executive and the Company cannot agree on the selection of an arbitrator, each Party shall select an arbitrator and the two arbitrators shall select a third arbitrator, and the three arbitrators shall form an arbitration panel that shall resolve the dispute by majority vote. Judgment upon the award

rendered by the arbitrator or arbitrators may be entered in any court having jurisdiction thereof. Costs of the arbitrator or arbitrators and other similar costs in connection with an arbitration shall be shared equally by the Parties; all other costs, such as attorneys' fees incurred by each Party, shall be borne by the Party incurring such costs.

20. NOTICES.

All notices that are required or permitted hereunder shall be in writing and sufficient if delivered personally, sent by facsimile (and promptly confirmed by personal delivery, registered or certified mail or overnight courier), sent by nationally-recognized overnight courier or sent by registered or certified mail, postage prepaid, addressed as follows:

If to the Company: Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210
Attn: Corporate Secretary

If to the Executive: at the Executive's home address listed in the Company records.

Any such notice shall be deemed to have been given: (a) when delivered if personally delivered or sent by facsimile on a business day; (b) on the business day after dispatch if sent by nationally-recognized overnight courier; and/or (c) on the fifth business day following the date of mailing if sent by mail.

21. HEADINGS.

The headings of the sections contained in this Agreement are for convenience only and shall not be deemed to control or affect the meaning or construction of any provision of this Agreement.

22. COUNTERPARTS.

This Agreement may be executed in two or more counterparts.

23. SECTION 409A OF THE CODE.

It is the intention of the Company and the Executive that this Agreement and the payments provided for herein are either exempt from or meet the requirements of Section 409A. The Company and the Executive agree to cooperate in good faith in preparing and executing such amendments to this Agreement, if any, as the Company or the Executive may reasonably request solely for the purpose of assuring that this Agreement and the payments provided hereunder remain exempt from or meet the requirements of Section 409A, as applicable. Nothing in this Agreement shall require the Company to increase the Executive's compensation or make the Executive whole for any such changes. In no event, however, shall the Company have any liability relating to the failure or alleged failure of any payment or benefit under this Agreement to comply with, or be exempt from, the requirements of Section 409A.

Each payment made under this Agreement shall be treated as a separate payment and the right to a series of installment payments under this Agreement is to be treated as a right to a series of separate payments. The Executive's right to payment or reimbursement for any expenses hereunder shall be subject to the following additional rules: (i) the amount of expenses eligible for payment or reimbursement during any calendar year shall not affect the expenses eligible for payment or reimbursement in any other calendar year, (ii) payment or reimbursement shall be made not later than December 31 of the calendar year following the calendar year in which the expense or payment was incurred, and (iii) the right to payment or reimbursement shall not be subject to liquidation or exchange for any other benefit.

24. CLAWBACK.

The payment of all amounts and the equity granted to the Executive by the Company pursuant to this Agreement or otherwise shall be subject to and shall be deemed amended hereby to incorporate any policy applicable to the executives of the Company adopted by the Company requiring the repayment of compensation paid or provided to the Executive.

25. TAX WITHHOLDING; NO GUARANTEE OF ANY TAX CONSEQUENCES.

All payments hereunder shall be subject to all applicable withholding for any federal, state or local income taxes including any excise taxes under the Code. Notwithstanding any other provision of this Agreement to the contrary or other representation, the Company does not in any way guarantee the tax consequences of any payment or compensation under this Agreement including, without limitation, under Section 409A.

IN WITNESS WHEREOF, the undersigned have executed this Agreement as of the date first written above.

Vertex Pharmaceuticals Incorporated

/s/ Reshma Kewalramani

_____

Name: Reshma Kewalramani
Title: CEO and President

Executive

/s/ Nia Tatsis

_____

Name: Nia Tatsis

VERTEX PHARMACEUTICALS INCORPORATED
50 NORTHERN AVENUE BOSTON, MA 02210
TEL. 617.341.6100

August 1, 2020

Nia Tatsis
[Address]

RE: Change of Control Agreement

Dear Nia:

You are a key member of the senior management team of Vertex Pharmaceuticals Incorporated (the "Company"). As a result, the Company would like to provide you with the following "change of control" benefits to help ensure that if the Company becomes involved in a "change of control" transaction, there will be no distraction from your attention to the needs of the Company.

I. *Definitions*. For the purposes of this Change of Control Agreement (this "Agreement"), capitalized terms used herein shall have the following meanings:

1. "Cause" shall mean:

(a) your conviction of a crime involving moral turpitude;

(b) your willful refusal or failure to follow a lawful directive or instruction of the Company's Board of Directors or the individual(s) to whom you report, provided that you receive prior written notice of the directive(s) or instruction(s) that you failed to follow, and provided further that the Company, in good faith, gives you 30 days to correct such failure and further provided that if you correct the failure(s), any termination of your employment on account of such failure shall not be treated for purposes of this Agreement as a termination of employment for "Cause";

(c) your material breach of the Company's insider trading policy or of any provision of the Employment Agreement entered into between you and the Company on the date hereof (the "Employment Agreement") or the agreement between you and the Company entitled "Employee Non-Disclosure, Non-Competition and Inventions Agreement" dated as of July 23, 2017 (the "Inventions Agreement"); or

(d) your breach of the code of conduct or any other material policy of the Company or any of its affiliates that is damaging to the financial condition or reputation of the Company or any of its affiliates.

2. "Change of Control" shall mean that:

(a) any "person" or "group" as such terms are used in Sections 13(d) and 14(d)(2) of the Securities Exchange Act of 1934, as amended (the "Act"), becomes a beneficial owner, as such term is used in Rule 13d-3 promulgated under the Act, of securities of the Company representing more than 50% of the combined voting power of the outstanding securities of the Company having the right to vote in the election of directors; or

(b) all or substantially all the business or assets of the Company are sold or disposed of, or the Company or a subsidiary of the Company combines with another company

pursuant to a merger, consolidation, or other similar transaction, other than (i) a transaction solely for the purpose of reincorporating the Company or one of its subsidiaries in a different jurisdiction or recapitalizing or reclassifying the Company's stock; or (ii) a merger or consolidation in which the shareholders of the Company immediately prior to such merger or consolidation continue to own at least a majority of the outstanding voting securities of the Company or the surviving entity immediately after such merger or consolidation.

3. "Code" shall mean the Internal Revenue Code of 1986, as amended.

4. "Disability" shall mean a disability as determined under the Company's long-term disability plan or program in effect at the time the disability first occurs, or if no such plan or program exists at the time of disability, then a "disability" as defined under Section 22(e)(3) of the Code.

5. "Good Reason" shall mean one of the following events has occurred without your consent:

   (a) you suffer a material reduction in the authorities, duties or job title and responsibilities associated with your position as an Executive Vice President of the Company;

   (b) your annual base salary is decreased;

   (c) the office to which you are assigned is relocated to a place 35 or more miles away; or

   (d) following a Change of Control, the Company's successor fails to assume the Company's rights and obligations under this Agreement;

   provided that Good Reason shall not exist unless and until within 30 days after the event giving rise to Good Reason under (a), (b), (c) or (d) above has occurred, you deliver a written termination notice to the Company stating that an event giving rise to Good Reason has occurred and identifying with reasonable detail the event that you assert constitutes Good Reason under (a), (b), (c) or (d) above and the Company fails or refuses to cure or eliminate the event giving rise to Good Reason on or within 30 days after receiving your notice. To avoid doubt, the termination of your employment will become effective at the close of business on the thirtieth day after the Company receives your termination notice, unless the Company cures or eliminates the event giving rise to Good Reason prior to such time.

6. "Termination Date" shall mean the last day of your employment with the Company.

II. *Severance Benefits upon Change of Control*. If:

   (A) your employment is terminated by the Company (except for termination for Cause or due to a Disability or death) and the Termination Date is within 90 days prior to a Change of Control or within 12 months after a Change of Control; or

   (B) you (i) terminate your employment for Good Reason (in accordance with the notice and cure provisions set forth in Section I.5 above) and (ii) the

event giving rise to Good Reason occurs within 90 days prior to a Change of Control or within 12 months after a Change of Control;

then, you shall receive the following benefits:

1. *Severance Payment*. In exchange for your execution of a general release, in a form satisfactory to the Company, of all claims against the Company, its subsidiaries, and its and their officers, directors and representatives, that becomes enforceable and irrevocable within the 60-day period following the Termination Date, the Company shall make a cash payment (the "Severance Payment") to you in an amount equal to the sum of:

   (a) (i) your annual base salary (provided, however, that if you terminate your employment for Good Reason based on a reduction in your annual base salary, then the annual base salary to be used in calculating the Severance Payment shall be your annual base salary in effect immediately prior to such reduction in annual base salary) plus (ii) your target bonus under any bonus program applicable to you for the year in which the Termination Date occurs; plus

   (b) a pro rata portion of your target bonus for the portion of the year in which the Termination Date occurs under any bonus program applicable to you, calculated based on the number of days you were employed during such year; plus

   (c) all other cash incentive compensation awards earned by you but not paid prior to the Termination Date; provided that, if a fiscal year has been completed and the incentive award for such fiscal year has not been determined, the incentive compensation for such completed fiscal year shall equal the target bonus for such fiscal year.

   Except with respect to any portion of the Severance Payment that is delayed as set forth in this paragraph, the Severance Payment shall be made in cash within ten days after the execution by you of the general release referred to above and expiration without revocation of any applicable revocation periods under such general release (or, if the Change of Control resulting in your becoming entitled to such benefits occurs after such execution and expiration, within ten days after the Change of Control), provided that, if the 60-day period during which the general release is required to become effective and irrevocable begins in one calendar year and ends in another calendar year, the Severance Payment shall not be made before the first day of the second calendar year.

   If you are a "specified employee" (as defined below) on the Termination Date, the commencement of the delivery of any such payments that constitute nonqualified deferred compensation payable upon a "separation from service" (as defined below) will be delayed until the first business day that is more than six months after your Termination Date. The determination of whether, and the extent to which, any of the payments to be made to you hereunder are nonqualified deferred compensation shall be made after the application of all applicable exclusions, including those set forth under Treasury Reg. § 1.409A-1(b)(9) and Treasury Reg. § 1.409A-1(a)(5). For purposes of this Agreement, to the extent required to ensure compliance with Section 409A of the Code, all references to "termination of employment" and correlative phrases shall be construed to require a "separation from service" (as defined in Treasury Reg. §1.409A-1(h) after giving effect to the presumptions contained therein), and the term "specified employee" means an individual determined by the Company to be a specified employee under Treasury Reg.

§1.409A-1(i). Each payment made under this Agreement shall be treated as a separate payment and the right to a series of installment payments under this Agreement is to be treated as a right to a series of separate payments. Your right to payment or reimbursement for any expenses hereunder that would constitute nonqualified deferred compensation subject to Section 409A of the Code will be subject to the following additional rules: (i) the amount of expenses eligible for payment or reimbursement during any calendar year shall not affect the expenses eligible for payment or reimbursement in any other calendar year, (ii) payment or reimbursement shall be made not later than December 31 of the calendar year following the calendar year in which the expense or payment was incurred, and (iii) the right to payment or reimbursement shall not be subject to liquidation or exchange for any other benefit.

2. *Accelerated Vesting.*

(a) On the Termination Date, stock options for the purchase of the Company's securities held by you as of the Termination Date and not then vested and exercisable shall immediately become vested and exercisable in full. The options to which this accelerated vesting applies shall remain exercisable until the earlier of (a) the end of the 90-day period immediately following the later of (i) the Termination Date or (ii) the date of the Change of Control and (b) the date the stock option(s) would otherwise expire; and

(b) On the Termination Date, each outstanding restricted stock unit grant shall be accelerated and the Shares shall be delivered to you within two business days (subject to (i) your making satisfactory arrangements with the Company providing for the payment to the Company of all required withholding taxes and (ii) with the number of shares subject to the restricted stock unit grants that contain performance criteria vesting at target or, if the applicable performance criteria have already been certified, based on earned shares or units as set forth in the applicable restricted stock unit grant agreement).

If your employment terminates during the 90-day period prior to a Change of Control, the accelerated vesting and settlement, if applicable, set forth above shall become effective immediately prior to such Change of Control. Notwithstanding anything to the contrary in this Agreement, the terms of any option agreement or restricted stock unit agreement shall govern the acceleration, if any, of vesting and period of exercisability of such awards, as applicable, except to the extent that the terms of this Agreement are more favorable to you.

3. *Continued Insurance Coverage*. If COBRA coverage is elected by you, the Company shall pay the cost of insurance continuation premiums on your behalf (whether or not covered by COBRA) to continue standard medical, dental and life insurance coverage for you (or the cash equivalent of same if you are ineligible for continued coverage), on a monthly basis, until the earlier of (i) the date 12 months after the Termination Date or (ii) the date you begin receiving substantially equivalent coverage and benefits through a subsequent employer.

4. *No Mitigation.* You shall not be required to mitigate the amount of the Severance Payment or any other benefit provided under this Agreement by seeking other employment or otherwise, nor shall the amount of any payment or benefit provided for in this Agreement be reduced (except as provided in Article II Section 3(ii)) by any compensation earned by you as the result of other employment, by retirement benefits, or

be offset against any amount claimed to be owed by you to the Company or otherwise (except for any required withholding taxes); provided, that if the Company makes any other severance payments to you under any other program or agreement, including the Employment Agreement, such amounts shall be offset against the payments the Company is obligated to make pursuant to this Agreement.

III. *Miscellaneous.*

1. *Employee's Obligations*. Upon termination of employment, you shall promptly deliver to the Company all property of the Company and all material documents, statistics, account records, programs and other similar tangible items which may by in your possession or under your control and which relate to the business or affairs of the Company or its subsidiaries, and no copies of any such documents or any part thereof shall be retained by you.

2. *Entire Agreement*. This Agreement, the Employment Agreement and the Inventions Agreement executed by you covers the entire understanding of the parties as to the subject matter hereof, superseding all prior understandings and agreements related hereto. No modification or amendment of the terms and conditions of this Agreement shall be effective unless in writing and signed by the parties or their respective duly authorized agents, provided, however, that the Company may, without your consent, unilaterally adopt amendments that may be required so that this Agreement continues to comply with applicable law or regulation, including without limitation Section 409A of the Code, provided such amendments do not adversely affect the benefits to be provided to you under Section II of this Agreement. In no event shall the Company have any liability relating to the failure or alleged failure of any payment or benefit under this Agreement to comply with or be exempt from, the requirements of Section 409A of the Code.

3. *Governing Law*. This Agreement shall be governed by the laws of The Commonwealth of Massachusetts, as applied to contracts entered into and performed entirely in Massachusetts by Massachusetts residents.

4. *Successors and Assigns*. This Agreement may be assigned by the Company upon a sale, transfer or reorganization of the Company. Upon a Change of Control, the Company shall require the successor to assume the Company's rights and obligations under this Agreement. The Company's failure to do so shall constitute Good Reason and a material breach of this Agreement. This Agreement shall be binding upon and inure to the benefit of the parties hereto and their successors, permitted assigns, legal representatives and heirs.

Kindly indicate your acceptance of the foregoing by signing and dating this Agreement as noted below, and returning one fully executed original to my attention.

Very truly yours,

Vertex Pharmaceuticals Incorporated

By: /s/ Reshma Kewalramani
Name: Reshma Kewalramani
Title: CEO and President

ACCEPTED AND AGREED:

/s/ Nia Tatsis

Nia Tatsis

Vertex Pharmaceuticals Incorporated Annual Non-Employee Board Compensation

Annual Retainer	$100,000
Committee Chair Compensation	
Audit & Finance Committee Chair	$30,000 annual retainer
Management Development & Compensation Committee Chair	$25,000 annual retainer
Corporate Governance & Nominating Committee Chair	$25,000 annual retainer
Science & Technology Committee Chair	$25,000 annual retainer
Committee Membership Fee (Non-Chairs)	
Audit & Finance Committee Member	$15,000 annual retainer
Management Development & Compensation Committee Member	$12,500 annual retainer
Corporate Governance & Nominating Committee Member	$10,000 annual retainer
Science & Technology Committee Member	$10,000 annual retainer
Lead Independent Director Compensation	$40,000 annual retainer

Annual Equity Grants

Annually on May 1, $400,000 in value-based awards, comprised at the director's election of restricted stock units and/or options

- Options are fully vested upon grant
- Restricted stock units cliff vest on the 1 year anniversary of the grant date

Initial Equity Grants

On date director joins the board of directors, a $400,000 restricted stock unit award that vests on the first anniversary of the grant date.

Each of our non-employee directors is eligible to defer the cash and restricted stock portion of his/her compensation set forth above and elect to receive deferred stock units that convert to common stock in specified circumstances.

Exhibit 21.1

Subsidiaries of Vertex Pharmaceuticals Incorporated

Vertex Pharmaceuticals (San Diego) LLC, a Delaware limited liability company

Vertex Securities Corporation, a Massachusetts corporation

Vertex Pharmaceuticals (Distribution) Incorporated, a Delaware corporation

Vertex Pharmaceuticals (Cayman) Limited, a Cayman Islands company (3)

Vertex Pharmaceuticals (Cayman III) Limited, a Cayman Islands company (5)

Vertex Pharmaceuticals (Cayman 509) Limited, a Cayman Islands company

Vertex Pharmaceuticals (Cayman 765) Limited, a Cayman Islands company

Vertex Pharmaceuticals (Cayman 787) Limited, a Cayman Islands company

Vertex Pharmaceuticals (Delaware) LLC, a Delaware limited liability company

Vertex Pharmaceuticals (Puerto Rico) LLC, a Delaware limited liability company

Vertex Pharmaceuticals (Canada) Incorporated, a Canadian company (1)

Vertex Pharmaceuticals (Singapore) Pte. Ltd., a Singapore company

Vertex Holdings, Inc., a Delaware corporation

Vertex Pharmaceuticals (Europe) Limited, a United Kingdom company (5)

Vertex Pharmaceuticals (Ireland) Limited, an Irish company (6)

Vertex Pharmaceuticals (U.K.) Limited, a United Kingdom company (6)

Vertex Pharmaceuticals (France) SAS, a French company

Vertex Pharmaceuticals (Germany) GmbH, a German company

Vertex Pharmaceuticals (Australia) Pty. Ltd., an Australian company

Vertex Pharmaceuticals (Spain), S.L., a Spanish company

Vertex Pharmaceuticals (Netherlands) B.V., a Dutch company

Vertex Pharmaceuticals (Italy) S.r.L., an Italian company

Vertex Farmaceutica do Brasil LTDA, a Brazilian company (4)

Vertex Pharmaceuticals GmbH, an Austrian company (6)

Vertex Pharmaceuticals (Portugal), Unipessoal Lda., a Portuguese company (6)

Vertex Pharmaceuticals (CH) GmbH, a Swiss company (6)

Vertex Pharmaceuticals (Sweden) AB, a Sweden company (6)

Vertex Pharmaceuticals Single Member Societe Anonyme, a Greek company (6)

Vertex Pharmaceuticals (Poland) sp. z.o.o (5) (6)

The Vertex Foundation, Inc., a Delaware corporation

Torreyana Insurance Company, Inc., a Vermont corporation

Vertex Pharmaceuticals (Czech Republic) s.r.o (6)

Vertex Pharmaceuticals (Belgium) BV (6)

---

(1) a subsidiary of Vertex Pharmaceuticals (Delaware) LLC
(2) a subsidiary of Vertex Pharmaceuticals (Singapore) Pte. Ltd.
(3) a subsidiary of Vertex Holdings, Inc.
(4) a subsidiary of Vertex Pharmaceuticals (UK) Limited
(5) a subsidiary of Vertex Pharmaceuticals (Cayman) Limited
(6) a subsidiary of Vertex Pharmaceuticals (Europe) Limited

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the following Registration Statements:

(1) Registration Statement (Form S-3 No. 333-229656) of Vertex Pharmaceuticals Incorporated,

(2) Registration Statements (Form S-8 Nos. 333-134482, 333-150946, 333-160442, 333-166803 and 333-184787) pertaining to the Vertex Pharmaceuticals Incorporated Amended and Restated 2006 Stock and Option Plan (formerly known as the Vertex Pharmaceuticals Incorporated 2006 Stock and Option Plan),

(3) Registration Statements (Form S-8 Nos. 333-184784 and 333-232945) pertaining to the Vertex Pharmaceuticals Incorporated Employee Stock Purchase Plan, and

(4) Registration Statements (Form S-8 Nos. 333-226363, 333-219559, 333-188737, 333-197466, 333-206075 and 333-232948) pertaining to the Amended and Restated Vertex Pharmaceuticals Incorporated 2013 Stock and Option Plan (formerly known as the Vertex Pharmaceuticals Incorporated 2013 Stock and Option Plan);

of our reports dated February 9, 2022, with respect to the consolidated financial statements of Vertex Pharmaceuticals Incorporated and the effectiveness of internal control over financial reporting of Vertex Pharmaceuticals Incorporated, included in this Annual Report (Form 10-K) of Vertex Pharmaceuticals Incorporated for the year ended December 31, 2021.

/s/ Ernst & Young LLP

Boston, Massachusetts
February 9, 2022

Exhibit 31.1

CERTIFICATION

I, Reshma Kewalramani, certify that:

1. I have reviewed this Annual Report on Form 10-K of Vertex Pharmaceuticals Incorporated;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 9, 2022

/s/ Reshma Kewalramani

Reshma Kewalramani

Chief Executive Officer and President

Exhibit 31.2

CERTIFICATION

I, Charles F. Wagner, Jr., certify that:

1. I have reviewed this Annual Report on Form 10-K of Vertex Pharmaceuticals Incorporated;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 9, 2022

/s/ Charles F. Wagner, Jr.

Charles F. Wagner, Jr.
Executive Vice President and Chief Financial Officer

Exhibit 32.1

SECTION 906 CEO/CFO CERTIFICATION

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 (Subsections (a) and (b) of Section 1350, Chapter 63 of Title 18, United States Code) each of the undersigned officers of Vertex Pharmaceuticals Incorporated, a Massachusetts corporation (the "Company"), does hereby certify, to such officer's knowledge, that:

The Annual Report on Form 10-K for the year ended December 31, 2021 (the "Form 10-K") of the Company fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, and the information contained in the Form 10-K fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 9, 2022

/s/ Reshma Kewalramani

Reshma Kewalramani
Chief Executive Officer and President

Date: February 9, 2022

/s/ Charles F. Wagner, Jr.

Charles F. Wagner, Jr.
Executive Vice President and Chief Financial Officer