VERTEX PHARMACEUTICALS INC / MA
Form 10-K
February 13, 2019

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

FORM 10-K

x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the Fiscal Year Ended December 31, 2018

or

o 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	Name of Each Exchange on Which Registered
Common Stock, $0.01 Par Value Per Share	The Nasdaq Global Select Market

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

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

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 x No o

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10 K. x

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, 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 x Accelerated filer o Non-accelerated filer o Smaller reporting company o
Emerging growth company o

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. o

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

The aggregate market value of the registrant's common stock held by non-affiliates of the registrant (without admitting that any person whose shares are not included in such calculation is an affiliate) based on the last reported sale price of the common stock on June 29, 2018 (the last trading day of the registrant's second fiscal quarter of 2018) was $42.5 billion. As of January 31, 2019, the registrant had 255,656,889 shares of common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the definitive Proxy Statement for the 2019 Annual Meeting of Shareholders to be held on June 5, 2019 are incorporated by reference into Part III of this Annual Report on Form 10-K.

VERTEX PHARMACEUTICALS INCORPORATED
ANNUAL REPORT ON FORM 10-K
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"We," "us," "Vertex" and the "Company" 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®" and "SYMKEVI®" are registered trademarks of Vertex. 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.

PART I

ITEM 1. BUSINESS

OVERVIEW

We invest in scientific innovation to create transformative medicines for people with serious diseases. Our business is focused on developing and commercializing therapies for the treatment of cystic fibrosis, or CF, and advancing our research and development programs in other diseases.

Cystic Fibrosis

Our goal is to develop treatment regimens that will provide benefits to all patients with CF and will enhance the benefits that currently are being provided to patients taking our medicines. Our marketed medicines are SYMDEKO/SYMKEVI (tezacaftor in combination with ivacaftor), ORKAMBI (lumacaftor in combination with ivacaftor) and KALYDECO (ivacaftor). These three medicines are collectively approved to treat approximately half of the 75,000 CF patients in North America, Europe and Australia.

We believe the triple combination regimens of next-generation correctors in combination with tezacaftor and ivacaftor that we are evaluating in Phase 3 clinical development could potentially provide benefits to all CF patients who have at least one F508del mutation in their cystic fibrosis transmembrane conductance regulator, or CFTR, gene (approximately 90% of all CF patients). This would provide (i) the first treatment for the underlying cause of CF for patients who have one copy of the F508del mutation in their CFTR gene and a second mutation that results in minimal CFTR function, whom we refer to as F508del/Min patients; and (ii) an improved treatment option for a majority of patients who are currently eligible for our products.

In the fourth quarter of 2018, we reported positive data from our Phase 3 clinical trials evaluating the triple combination of VX-659, tezacaftor and ivacaftor. In the first quarter of 2019, we expect to report data from the Phase 3 clinical trials evaluating the triple combination of VX-445, tezacaftor and ivacaftor and select the better of the two regimens for potential regulatory approval. We expect to submit a New Drug Application, or NDA, to the United States Food and Drug Administration, or FDA, for a triple combination regimen no later than mid-2019.

Research and Development

We invest in research and development in order to discover and develop transformative medicines for people with serious diseases. Our goal is to identify and develop new medicines by combining transformative advances in the understanding of human disease and in the science of therapeutics to dramatically advance human health. We have a number of earlier-stage development programs that we are conducting independently or in collaboration with third parties, including:

- Pain. We are evaluating VX-150, a NaV1.8 inhibitor, in Phase 2 clinical development as a potential treatment for pain. We have obtained proof-of-concept data from Phase 2 clinical trials evaluating VX-150 in acute, chronic inflammatory and neuropathic pain. We have an ongoing Phase 2b dose-ranging clinical trial in acute pain, which, if successful, could support the initiation of Phase 3 development.
- Sickle cell disease and beta-thalassemia. We are co-developing CTX001, an investigational gene editing treatment, for the treatment of beta-thalassemia and sickle cell disease, with CRISPR Therapeutics AG, or CRISPR. We recently initiated two Phase 1/2 clinical trials to evaluate CTX001.
- Alpha-1 Antitrypsin Deficiency. In December 2018, we initiated a Phase 1 clinical trial for a novel drug candidate that is a potential treatment for alpha-1 antitrypsin, or AAT, deficiency.

We plan to continue investing in our research and development programs and fostering scientific innovation. We have advanced research programs to identify additional drug candidates for CF, pain, and AAT deficiency, as well as other serious diseases, including focal segmental glomerulosclerosis, or FSGS. We also have a number of earlier-stage research programs directed at other serious diseases. We believe that pursuing research in diverse areas allows us to balance the risks inherent in drug development and may provide drug candidates that will form our pipeline in future years.

CYSTIC FIBROSIS

Background

CF is a life shortening genetic disease affecting approximately 75,000 people in North America, Europe and Australia. CF is caused by a defective or missing 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 of the two of the most prevalent mutations, the F508del mutation or the G551D 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. The G551D mutation results in a defect in the CFTR protein in which the defective protein reaches the surface of a cell but does not efficiently transport chloride ions across the cell membrane.

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 open probability of the CFTR protein channels on the cell surface, increasing the flow of salt and water into and out of the cell. CFTR correctors, such as lumacaftor, tezacaftor, VX-659 and VX-445, help CFTR proteins reach the cell surface.

Our Medicines

Our medicines, SYMDEKO/SYMKEVI, ORKAMBI and KALYDECO, are collectively approved to treat approximately half of the 75,000 CF patients in North America, Europe and Australia. Our approved medicines, including information regarding the applicable indication and the age groups for which the medicine has been approved, are set forth in the table below.

Product	Scientific Name	Region/ Initial Approval	Indication	Eligible Age Group
	ivacaftor/tezacaftor	U.S. (2018)	CF patients (i) homozygous for the F508del mutation or (ii) with one copy of certain mutations that result in residual CFTR activity	12 years of age and older
	ivacaftor/tezacaftor	European Union (2018)	CF patients (i) homozygous for the F508del mutation and (ii) with one copy of the F508del mutation and one copy of certain mutations that result in residual CFTR activity	12 years of age and older
	ivacaftor/lumacaftor	U.S. (2015)	CF patients homozygous for the F508del mutation	2 years of age and older
	ivacaftor/lumacaftor	European Union (2015)	CF patients homozygous for the F508del mutation	2 years of age and older
	ivacaftor	U.S. (2012)	CF patients with G551D and other specified mutations	1 year of age and older
	ivacaftor	European Union (2012)	CF patients with G551D and other specified mutations	1 year of age and older

In addition to the European Union and the United States, we market our products in additional countries, including Australia and Canada. We continuously seek to increase the number of patients eligible to receive our current medicines through label expansions. Activities in support of our label expansion efforts include:

- We have obtained positive data from a Phase 3 clinical trial evaluating tezacaftor in combination with ivacaftor in patients with CF six to eleven years of age who are F508del homozygous or who have one copy of the F508del mutation and one mutation that results in residual CFTR activity. The clinical trial met its primary safety endpoint,

and safety data showed that the combination was generally well tolerated. We submitted a supplemental new drug application, or sNDA, for these patients to the FDA in the fourth quarter of 2018. To support potential approval in the European Union, an eight-week Phase 3 clinical trial is ongoing to evaluate tezacaftor in combination with ivacaftor in approximately 65 children six to eleven years of age. The primary endpoint of the clinical trial is the absolute change in the lung clearance index.

- In October 2018, we announced positive data from a Phase 3 clinical trial of ivacaftor in patients with CF six to less than twelve months of age. We submitted a sNDA to the FDA and a line extension to the EMA in late 2018.

Triple Combination Programs

We believe the triple combination regimens of a next-generation corrector in combination with tezacaftor and ivacaftor that we are evaluating in Phase 3 clinical development could potentially provide benefits to all CF patients who have at least one F508del mutation in their cystic fibrosis transmembrane conductance regulator, or CFTR, gene (approximately 90% of all CF patients). The Phase 3 development programs for VX-659 and VX-445 that we initiated in the first half of 2018 are evaluating F508del/Min patients and F508del homozygous patients 12 years of age and older. We more recently initiated Phase 3 clinical trials for triple combinations containing VX-659 and VX-445 in F508del/Min and F508del homozygous patients who are six to eleven years of age.

Each of the VX-659 and VX-445 triple combination Phase 3 development programs in patients 12 years of age and older is comprised of two clinical trials. The first clinical trial in each program was designed to enroll approximately 360 F508del/Min patients. In the U.S., the primary efficacy endpoint of the first clinical trial in each program is the mean absolute change from baseline in percent predicted forced expiratory volume in one second, or ppFEV1, at week four of treatment with the triple combination regimen versus placebo. The second clinical trial in each program was designed to enroll approximately 100 F508del homozygous patients. The primary efficacy endpoint of the second clinical trial in each program is the mean absolute change from baseline in ppFEV1 at week four of treatment with the triple combination regimen compared to tezacaftor in combination with ivacaftor.

VX-659 Triple Combination Phase 3 Clinical Data

The triple combination of VX-659, tezacaftor and ivacaftor resulted in statistically significant improvements in lung function in two Phase 3 clinical trials. Data from a pre-specified interim analysis of the Phase 3 clinical trials in F508del/Min patients showed a mean absolute improvement in ppFEV1 of 14.0 percentage points from baseline at week 4 of treatment compared to placebo ($p<0.0001$). In the Phase 3 clinical trial in F508del homozygous patients, data demonstrated that the addition of VX-659 in patients already receiving tezacaftor and ivacaftor resulted in a mean absolute improvement in ppFEV1 of 10.0 percentage points from baseline at week 4 of treatment compared to the control group in whom placebo was added to tezacaftor and ivacaftor ($p<0.0001$). The VX-659 triple combination regimen was generally well tolerated, and the safety and efficacy profile from the results support the potential submission of an NDA for the VX-659 triple combination regimen.

Expected VX-445 Triple Combination Phase 3 Clinical Data

Enrollment is complete for the two Phase 3 clinical trials of the triple combination of VX-445, tezacaftor and ivacaftor in in F508del/Min patients and F508del homozygous patients. We expect to report data from both Phase 3 clinical trials of the VX-445 triple combination regimen in the first quarter of 2019.

Expected Regulatory Submissions

The data expected in the first quarter of 2019 for the VX-445 triple combination and the data reported in the fourth quarter of 2018 for the VX-659 triple combination are anticipated to enable us to choose the better of the two regimens to submit for potential global regulatory approvals. We believe these data will provide the basis for a submission of an NDA to the FDA for a triple combination regimen no later than mid-2019. Subsequent to the NDA filing, we intend to make regulatory submissions in markets outside the United States.

VX-121

In addition, we have initiated a Phase 1/2 clinical trial to evaluate VX-121, an additional next-generation corrector.

RESEARCH AND DEVELOPMENT PROGRAMS

We invest in research and development in order to discover and develop transformative medicines for people with serious diseases. Our goal is to identify and develop new medicines by combining transformative advances in the understanding of

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human disease with the science of therapeutics to dramatically advance human health. Our approach to drug discovery has focused on the research and development of small molecule drugs, which has been validated through our success in moving novel small molecule drug candidates into clinical trials and obtaining marketing approvals for KALYDECO, ORKAMBI and SYMDEKO/SYMKEVI for the treatment of CF and INCIVEK (telaprevir) for the treatment of hepatitis C infection. Over the last several years, we have expanded our research capabilities to include additional innovative therapeutic approaches with a focus on nucleic acid-based therapies. In addition to our approved medicines, we have a number of drug candidates that we are developing independently or that are being developed by collaborators pursuant to collaboration agreements.

We are applying the experience we gained developing medicines for CF to guide our current investments in research and development programs by:

- generating biological assays and identifying clinical biomarkers that we believe will be predictive of clinical responses;
- targeting the discovery and development of medicines that have the potential to offer transformative benefit;
- identifying efficient clinical and regulatory paths to bring new medicines to patients; and
- focusing on treatments for life-threatening diseases with a high unmet medical need.

In addition to continuing our research to identify additional drug candidates for the treatment of CF, we are focusing our research and development efforts on developing products for the treatment serious diseases including sickle cell disease, beta-thalassemia, pain, AAT deficiency, FSGS and other diseases.

To augment our internal programs, we seek to 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 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.

Pain

We are developing VX-150, an inhibitor of the sodium channel 1.8 (Nav 1.8), as a potential treatment for pain. We have obtained positive results from three Phase 2 clinical trials of VX-150:

- In the first quarter of 2017, we announced data from a 14-day Phase 2 randomized, double-blind, placebo-controlled, clinical trial of VX-150 in patients with chronic pain from osteoarthritis of the knee.
- In the first quarter of 2018, we announced data from a Phase 2 randomized, double-blind, placebo-controlled clinical trial evaluating VX-150 as a treatment for patients with acute pain following bunionectomy surgery.
- In the fourth quarter of 2018, we announced data from a Phase 2 randomized, double-blind, placebo-controlled clinical trial evaluating VX-150 as a treatment for patients with pain caused by small fiber neuropathy.

A Phase 2b dose-ranging study of VX-150 in patients with acute pain following bunionectomy surgery is currently ongoing to support potential pivotal development in acute pain. We have multiple pain molecules in late-stage preclinical development and plan to initiate clinical development of the first of these molecules in 2019.

Sickle Cell Disease and Beta-Thalassemia

We are co-developing CTX001, an investigational gene editing treatment, for the treatment of hemoglobinopathies, with CRISPR Therapeutics. Hemoglobinopathies are a group of inherited blood disorders that result from variations in the synthesis or structure of hemoglobin, a protein in red blood cells that delivers oxygen and removes carbon dioxide throughout the body. We are seeking to develop a CRISPR/Cas9-based therapy to treat both beta-thalassemia and sickle cell disease. These diseases are caused by mutations in the gene encoding the beta-globin protein, which is an essential component of hemoglobin.

We and CRISPR have initiated and are enrolling patients in Phase 1/2 clinical trials to evaluate CTX001 in beta-thalassemia and sickle cell disease. The first two patients in each clinical trial will be dosed sequentially and, pending data from these initial two patients, subsequent patients can be dosed concurrently.

Alpha-1 Antitrypsin Deficiency

We are seeking to develop medicines to treat AAT deficiency. In December 2018, we initiated a Phase 1 clinical trial for a novel drug candidate that is a potential treatment for AAT deficiency. AAT deficiency is a disease that affects approximately 100,000 people in the United States and Europe. AAT deficiency is caused by a defective AAT protein resulting from mutations in the SERPINA1 gene. To develop AAT deficiency, children must inherit two defective SERPINA1 alleles (one from each parent). The mutation results in a defect in the AAT protein in which the protein does not fold correctly. This folding defect can cause the AAT protein to accumulate in the liver (where it is produced), which can cause liver damage. As a result, sufficient levels of the protein fail to reach other organs, particularly the lungs, where it would typically protect them from the harmful effects of certain enzymes. This can cause damage to lung tissue and may lead to emphysema or chronic pulmonary obstructive disease, among other things.

Focal Segmental Glomerulosclerosis

We are conducting research to identify drug candidates to treat the underlying biology of FSGS, a kidney disease. FSGS is a rare disease that attacks the kidney's filtering units causing serious scarring that leads to permanent kidney damage. FSGS is a leading cause of nephrotic syndrome in children and kidney failure in adults. We may advance our first drug candidate for FSGS into clinical development in 2019.

Influenza

Janssen Pharmaceuticals, Inc., or Janssen, is developing pimodivir as a potential treatment for the influenza A virus. We exclusively licensed pimodivir to Janssen in 2014. Janssen is conducting Phase 3 clinical trials of pimodivir in combination standard of care treatment in patients who are hospitalized or are outpatients at a higher risk of influenza-related complications.

COMMERCIALIZATION OF OUR MEDICINES

Commercial Organization

Our commercial organization focuses on supporting sales of 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 and obtaining reimbursement for our products from third-party payors, including governmental organizations in the United States and ex-U.S. markets.

Our U.S. field-based CF commercial team is comprised of a small number of individuals whom we believe is sufficient to support commercialization of our medicines for CF. We focus our CF marketing efforts in the United States 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 United States focused on the treatment of CF. In international markets, we have small sales forces that promote KALYDECO, ORKAMBI and SYMKEVI in jurisdictions where these products are approved.

We market our products through personal interactions with physicians and allied health care professionals. In addition, 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 policy-makers. We also have established programs in the United States that provide our products to qualified uninsured or underinsured patients at no charge or at a reduced charge, based on specific eligibility criteria.

Reimbursement

Sales of our products depend, to a large degree, on the extent to which our products will be covered by third-party payors, such as government health programs, commercial insurance and managed health care organizations. These third-party payors increasingly are reducing reimbursements for 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. Decreases in third-party reimbursement for a product or a decision by a third-party payor to not cover a product could

reduce physician usage of the product.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, established the Medicare Part D program to provide 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. 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, 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 therapeutic committee. 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. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from the MMA may result in a similar reduction in payments from non-governmental payors.

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, 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. 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 is designed to expand and increase industry rebates for drugs covered under Medicaid programs, impose an annual fee on branded pharmaceutical manufacturers and make changes to the coverage requirements under the Medicare Part D program. The branded prescription drug fee is not tax deductible.

In Europe and many other foreign countries, the success of our products depends largely on obtaining and maintaining government reimbursement, because in many foreign countries, patients are unable to access prescription pharmaceutical products that are not reimbursed by their governments. Negotiating reimbursement rates in foreign countries can delay the commercialization of a pharmaceutical product and generally results in a reimbursement rate that is lower than the net price that companies can obtain for the same product in the United States.

In some countries, such as Germany and France, commercial sales of a new product can occasionally begin while the reimbursement rate that a company will receive is under discussion. In other countries, a company must complete the reimbursement discussions prior to the commencement of commercial sales of the pharmaceutical product. The requirements governing drug pricing vary widely from country to country. For example, the member states of the European Union can restrict the range of drugs for which their national health insurance systems provide reimbursement and can control the prices of drugs for human use. 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 profitability of the company placing the drug on the market. Recently, many countries in the European Union have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage healthcare expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the European Union. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will provide for reimbursement of our products, or such countries may only provide for reimbursement on terms that we do not deem adequate. Additionally, reimbursement discussions in ex-U.S. markets may take a significant period of time.

COLLABORATIONS AND STRATEGIC INVESTMENTS

As part of our business strategy, we seek to license or acquire drugs, drug candidates and other technologies that have the potential to complement our ongoing research and development efforts in CF, access emerging technologies and license or acquire pipeline assets with a focus on early-stage assets. In addition, we establish business relationships with collaborators to support our research activities and to lead or support development and/or commercialization of

certain drug candidates.

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 generally

have become responsible for the costs of research activities and obtained development and commercialization rights to resulting drug candidates. Depending on the terms of the arrangements, we 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 resulting from the collaboration. Alternatively, when we enter into a co-development arrangement, we generally agree to split costs and revenues associated with the relevant program. Our current in-license agreements include:

- CRISPR Therapeutics AG. 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 currently are co-developing CTX001 for the treatment of sickle cell disease and beta-thalassemia and, if successful, have agreed to co-commercialize CTX001. In addition, we are collaborating with CRISPR on additional research targets, including CF, and will have the option to exclusively license the resulting therapeutics for these targets.
- Arbor Biotechnologies, Inc. In the fourth quarter of 2018, we entered into a collaboration with Arbor Biotechnologies, pursuant to which we are focusing on the discovery of novel proteins, including DNA endonucleases, to advance the development of new gene-editing therapies.
- Moderna Therapeutics, Inc. In 2016, we entered into a collaboration with Moderna Therapeutics, pursuant to which we are seeking to identify and develop messenger ribonucleic acid, or mRNA, therapeutics for the treatment of CF.
- Other Arrangements. In 2018, we entered into agreements with Genomics plc, Merck KGaA, Darmstadt, Germany, and X-Chem, Inc. in order to support our research efforts.

Out-license Agreements

We have entered into various agreements pursuant to which we have out-licensed rights to certain drug 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 drug candidates and obtain development and commercialization rights to these drug 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:

- Janssen Pharmaceuticals, Inc. In 2014, we entered into an agreement with Janssen. Pursuant to this agreement, Janssen Inc. is developing pimodivir for the treatment of influenza. Janssen is evaluating pimodivir in Phase 3 clinical trials in patients with influenza A infection.
- Merck KGaA, Darmstadt, Germany. In 2017, we entered into a Strategic Collaboration and License Agreement with Merck KGaA, Darmstadt, Germany, pursuant to which we granted an exclusive worldwide license to research, develop and commercialize four oncology research and development programs.

Strategic Investments

In connection with our business development activities, we periodically make equity investments in our collaborators. We hold strategic equity investments in public companies including CRISPR and Moderna, as well as certain private companies, including Arbor Biotechnologies. We may make additional strategic equity investments in public or private companies in the future.

Cystic Fibrosis Foundation Therapeutics Incorporated

We have entered into collaborations with pharmaceutical and other companies and organizations that provided us financial and other resources, and that provided support for certain programs. In particular, in 2004 we entered into a collaboration agreement with 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 any approved drugs 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 VX-659 and VX-445. For combination products, such as ORKAMBI and SYMDEKO/SYMKEVI, 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 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 market 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. Market exclusivity runs concurrently with patent exclusivity.

We own or hold exclusive licenses to several hundred patents in the United States. We own eight issued U.S. patents that cover the active pharmaceutical ingredients in KALYDECO, its marketed formulations, and/or its approved indication. We own 16 issued U.S. patents that cover the active pharmaceutical ingredients in ORKAMBI, its marketed formulations, and/or its approved indication. We own 17 issued U.S. patents that cover the active pharmaceutical ingredients in SYMDEKO, its marketed formulation, and/or its approved indication.

The table below sets forth the year of projected expiration for the basic product patents or pending patent applications covering each of our approved products and our drug candidates that have progressed at least into Phase 3 clinical trials. For products that are combinations of two or more active ingredients, the projected expiration of the latest expiring patent or application covering any of the active pharmaceutical ingredients is provided. 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 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/Drug Candidate	Status of United States Patent (Projected Expiration)	Status of European Union Patent (Projected Expiration)
KALYDECO	Granted (2027)	Granted (2025) [1]
ORKAMBI	Granted (2030)	Granted (2026) [2]
SYMDEKO/SYMKEVI	Granted (2027)	Granted (2028) [3]
VX-659/tezacaftor/ivacaftor	Pending (2037)	Pending (2037)
VX-445/tezacaftor/ivacaftor	Pending (2037)	Pending (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] We intend to apply in certain European countries for supplementary protection certificates for SYMKEVI, which we expect to expire in 2033.

In addition to our later-stage programs and marketed products, we actively monitor and file patent applications in the United States and in foreign countries on technology that is in the pre-clinical and early clinical stages. For example, we also own U.S. and foreign patents and patent applications covering the following:

- CF potentiators and correctors and many other related compounds, and the use of those compounds to treat CF.
- VX-150 and the use of VX-150 to treat pain indications.
- Other pre-clinical and clinical drug candidates and the use of such drug 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 cannot be certain, however, that issued patents will be enforceable or provide adequate protection or that pending patent applications will result in issued patents.

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.

MANUFACTURING

As we market and sell our approved products and advance our drug 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 an international network of third parties to manufacture and distribute our products for commercial sale and post-approval clinical trials and to manufacture and distribute our drug candidates for clinical trials. In addition to establishing supply chains for each new approved product, we need to adapt our supply chain for existing products to include additional formulations that are often required in order to treat younger patients. We currently are focused on finalizing the supply chain that will be required in order to commercialize our triple combination regimens, if approved, and ensuring the stability of the supply chains for our current products.

We expect that we will continue for the foreseeable future to rely on third parties to meet our commercial supply needs and a significant portion of our clinical supply needs. We have established our own small-scale manufacturing capabilities in Boston, which we use for clinical trial and commercial supplies.

Our supply chain for sourcing raw materials and manufacturing drug product ready for distribution 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. Establishing and managing this global supply chain for each of our drugs and drug candidates requires a significant financial commitment and the creation and maintenance of numerous third-party contractual relationships. To ensure the stability of our supply chains we aim to develop additional sources of manufacture for all steps of our manufacturing processes at the time of, or shortly after, marketing approval. Therefore, at any point in time, we may have a limited number of single source manufacturers for certain steps in our manufacturing processes, particularly for recently launched products.

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 developed systems and processes to track, monitor and oversee 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 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.

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. Some of our competitors have substantially greater financial, technical 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 drug 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 drug

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 drug 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.

Cystic Fibrosis

A number of companies are seeking to identify and develop drug candidates for the treatment of CF, including public companies such as AbbVie, Eloxx Pharmaceuticals, ProQR Therapeutics, Proteostasis Therapeutics, and Translate Bio, and several private companies. Although we are the first company to successfully develop medicines that treat the underlying cause of CF, our products are collectively approved to treat only a portion of patients with CF and we believe that future treatment regimens, including our triple combination regimens, could deliver enhanced benefits to patients who are currently being treated with our medicines. Our competitors have research and development programs directed at identifying and developing CFTR potentiators, CFTR correctors and drug candidates with other mechanisms of action or that utilize new therapeutic approaches that seek to address the underlying cause of CF. Our competitors are exploring the development of drug candidates primarily as part of combination regimens of small molecules, and some competitors are exploring development of new therapeutic approaches, including nucleic acid-based therapies, which could provide a one-time treatment option for patients with CF. 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. If one or more competing therapies are successfully developed as a treatment for patients with CF, our revenues from our current products and/or additional CF products, if then approved, could face significant competitive pressure.

GOVERNMENT REGULATION

Our operations and activities are subject to extensive regulation by numerous government authorities in the United States, the European Union and other countries. In the United States, the European Union and other countries, drugs are subject to rigorous regulations governing the testing, manufacture, labeling, storage, record keeping, approval, advertising and promotion of our products. As a result of these regulations, product development and product approval processes are very expensive and time consuming. The regulatory requirements applicable to drug 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 Approval Processes

The process required by the FDA before a drug may be marketed in the United States 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 application, which must become effective before clinical trials in the United States may begin;
- performance of adequate and well-controlled clinical trials according to Good Clinical Practices, or GCP, to establish the safety and efficacy of the proposed drug for its intended use;
- submission to the FDA of an NDA;
- satisfactory completion of an 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.

Once a drug candidate 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 candidate in humans.

Preclinical or nonclinical testing typically continues even after the IND is submitted.

If the FDA accepts the IND, the drug candidate can then be studied in human clinical trials to determine if the drug candidate is safe and effective. These 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 initially is introduced into healthy human subjects and tested for safety, dosage tolerance, absorption, metabolism, distribution and elimination. In the case of some drug candidates for severe or life-threatening diseases, such as cancer, especially when the drug candidate 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 initiated in a limited patient population intended to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the drug candidate for specific targeted diseases 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 candidate and provide an adequate basis for regulatory approval and product labeling.

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 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. All clinical trials must be conducted under the supervision of one or more qualified investigators in accordance with GCP. Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently in other situations, including the occurrence of serious adverse events. Information about certain clinical trials must be submitted within specific time-frames to the National Institutes of Health for public dissemination on the www.clinicaltrials.gov website.

The results of drug development, preclinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests conducted on the chemistry of the drug candidate, proposed labeling and other relevant information are submitted to the FDA as part of an NDA requesting approval to market the drug candidate. The FDA reviews each NDA 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 for filing.

Once the submission is accepted for filing, the FDA begins an in-depth review. The FDA reviews an NDA to determine, among other things, whether a drug candidate is safe and effective for its intended use and whether its manufacturing is cGMP-compliant to assure and preserve the drug candidate’s identity, strength, quality and purity. The FDA may refer the NDA to an advisory committee for review and recommendation as to whether the NDA 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, the FDA will inspect the facility or facilities where the drug candidate is manufactured and tested. Additionally, before approving an NDA, 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 in its present form.

Biologics License Application Process

Certain of our drug candidates may be regulated by the FDA under the Food, Drug, and Cosmetic Act, or FDCA, and the Public Health Service Act as biologics. Biologics can present special safety, efficacy and manufacturing challenges that may differ from those present in the regulation of small molecule drugs. As such, while similar to the NDA review process described above, in lieu of filing an NDA, biologics require the submission of a Biologics License Application, or BLA, and approval of such BLA by the FDA prior to being marketed in the U.S.

Expedited Review and Approval

The FDA has developed four distinct approaches to make new drugs 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 or life-threatening 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

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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.

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 that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint. For drugs and biologics that have been designated as Breakthrough Therapies, robust FDA-sponsor interaction and communication can help to identify the most efficient and expeditious path for clinical development while minimizing the number of patients placed in ineffective control regimens.

The FDA may grant “priority review” status to products 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. In complying with cGMP, manufacturers must devote substantial time, money and effort in the areas of production, quality control and quality assurance to maintain 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 enforcement action may be taken, which may include a warning letter 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 standards 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 United States 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. 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 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 manufactured or distributed by us 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 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:

- 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 other safety-related limitations;
- warning letters or "untitled letters";
- product seizures;
- total or partial suspension of production or distribution; or
- injunctions, fines, disgorgement, refusals of government contracts, or civil or criminal penalties.

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

Biologics are also entitled to exclusivity under the Biologics Price Competition and Innovation Act, which was passed as Title VII to the Patient Protection and Affordable Care Act, or the ACA. The law provides a pathway for approval of biosimilars following the expiration of 12 years of exclusivity for the innovator biologic and a potential additional 180 day-extension term for conducting pediatric studies. 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 those efforts continue in 2019 and if the ACA is repealed, substantially modified, or invalidated, it is unclear what, if any, impact such action would have on biosimilar regulation.

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drug candidates intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 people in the United States. KALYDECO, ORKAMBI and SYMDEKO have been granted designation as orphan drugs by the FDA.

If a drug candidate that has orphan drug designation subsequently receives the first FDA approval for that drug 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 drug candidates for seven years if a competitor first obtains approval of the same product as defined by the FDA or if our drug candidate is determined to be contained within the competitor's product for the same indication or disease.

Foreign Regulation

We conduct clinical trials and market our products in numerous jurisdictions outside the United States. Most of these jurisdictions have clinical trial, product approval and post-approval regulatory processes that are similar in principle to those in the United States. Thus, whether or not we obtain FDA approval for a drug candidate, we must obtain approval by the comparable regulatory authorities of foreign countries or economic areas, such as the European Union, 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 European Union regulatory systems, a company may submit marketing authorization applications either under a centralized or decentralized procedure. The centralized procedure, which is compulsory for medicines produced by biotechnology or 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 European Union member states. In addition to the centralized procedure, Europe 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 anti-kickback laws and false claims laws. Anti-kickback laws make it illegal to solicit, offer, receive or pay any remuneration in exchange 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 program. False claims laws prohibit 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 false claims laws may also arise when a violation of certain laws or regulations related to the underlying products (e.g., violations regarding improper promotional activity 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 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 or require disclosure to the government and public of such interactions. The laws include 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 ambiguous requirements. Outside the United States, 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 United Kingdom generally will be subject to the Bribery Act.

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 data privacy and protection, 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. The extent of government regulation, which might result from future legislation or administrative action, cannot accurately be predicted.

EMPLOYEES

As of December 31, 2018, we had approximately 2,500 employees, as compared to approximately 2,300 employees as of December 31, 2017. Of these employees, approximately 2,000 were based in the United States and approximately 500 were based outside the United States. Our employees are not covered by a collective bargaining agreement, except for a small number of employees outside the United States.

A key aspect of remaining competitive in our industry is recruiting and retaining employees, including employees with the scientific and technical expertise to conduct our research activities and advance our development programs and commercial expertise to effectively marketing our products. We consider our relations with our employees to be good and over the last several years have successfully recruited talented and diverse employees to support our expanding business. However, we continue to face intense competition for our personnel from our competitors and other companies throughout our industry and from universities and research institutions.

OTHER MATTERS

Financial Information and Significant Customers

Financial information about our revenue by product and major customers is set forth in Note R, “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.

DIRECTORS AND EXECUTIVE OFFICERS OF THE REGISTRANT

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

Name	Age	Position
Jeffrey M. Leiden, M.D., Ph.D.	63	Chairman of the Board, Chief Executive Officer and President
David Altshuler, M.D., Ph.D.	54	Executive Vice President, Global Research and Chief Scientific Officer
Stuart A. Arbuckle	53	Executive Vice President and Chief Commercial Officer
Reshma Kewalramani, M.D.	46	Executive Vice President, Global Medicines Development and Medical Affairs, and Chief Medical Officer
Michael Parini, J.D.	44	Executive Vice President and Chief Legal and Administrative Officer
Amit K. Sachdev, J.D.	51	Executive Vice President and Chief Regulatory Officer
Paul M. Silva	52	Senior Vice President and Corporate Controller and Interim Chief Financial Officer
Sangeeta M. Bhatia, M.D., Ph.D.	50	Director
Alan Garber, M.D., Ph.D.	63	Director
Terrence C. Kearney	64	Director
Yuchun Lee	53	Director
Margaret G. McGlynn	59	Director
Bruce I. Sachs	59	Director
	71	Director

Elaine S. Ullian	74	Director
William Young		

Dr. Leiden is our Chairman, Chief Executive Officer and President. He has held the positions of Chief Executive Officer and President since February 2012 after joining us as CEO Designee in December 2011. 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 serves as a director of Quest Diagnostics Inc., a medical diagnostics company, and 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. 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, 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 and Chief Commercial Officer, a position he has held since September 2012. Prior to joining us, Mr. Arbuckle held multiple commercial leadership roles at Amgen, Inc., a 17,000 person biotechnology company, 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. Mr. Arbuckle holds a BSc in pharmacology and physiology from the University of Leeds.

Dr. Kewalramani is our Executive Vice President and Chief Medical Officer, a position she has held since April 2018. 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. Dr. Kewalramani is the industry representative to the FDA's Endocrine and Metabolic Drug Advisory Committee. 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.

Mr. Parini is our Executive Vice President and Chief Legal and Administrative Officer, a position he has held since January 2017. From January 2016 to January 2017, he was our Executive Vice President and Chief Legal Officer. From 2004 until he joined Vertex, Mr. Parini served in various roles of increasing responsibility at Pfizer Inc., a pharmaceutical company, most recently as Senior Vice President and Associate General Counsel. Prior to Pfizer, Mr. Parini was an attorney at Akin, Gump, Strauss, Hauer & Feld, L.L.P. Mr. Parini holds a B.A. from Georgetown University and a J.D. from the Georgetown University Law Center.

Mr. Sachdev is our Executive Vice President and Chief Regulatory Officer, a role he assumed in January 2017. He served as our Executive Vice President, Policy, Access and Value, from October 2014 through December 2016. 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. From 2010 through 2013 he established our first international commercial operations in Canada. 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 United States House of Representatives and practiced law at the Chemical Manufacturers Association, and subsequently at the law firm of Ropes & Gray LLP. Mr. Sachdev holds a B.S from Carnegie Mellon University, and a J.D. from Emory University School of Law.

Mr. Silva is our Senior Vice President and Corporate Controller, a position he has held since April 2011. In January 2019, Mr. Silva was appointed our interim Chief Financial Officer. Mr. Silva joined us in August 2007 as Senior Director, Accounting Operations and was our Vice President and Corporate Controller from September 2008 through April 2011. Prior to joining us, he was the Vice President, Internal Reporting at Iron Mountain Incorporated from July 2006 until August 2007 and a consultant to Iron Mountain's finance department from April 2005 until July 2006. He was the Finance Director of the Bioscience Technologies Division of Thermo Electron Corporation from 2002 to April 2005. Mr. Silva holds a B.S. in accounting from Assumption College.

Dr. Bhatia has been a member of our Board of Directors since June 2015. Dr. Bhatia is a professor at the Massachusetts Institute of Technology, or MIT, where she currently serves as the John J. and Dorothy Wilson Professor of Health Sciences & Technology/Electrical Engineering & Computer Science. For the 2018 year, Dr. Bhatia was on sabbatical from MIT as she served as a co-founder of Glympse Bio, a private company focused on developing in vivo sensing technology dedicated for disease monitoring. Prior to joining the Massachusetts Institute of Technology in 2005, Dr. Bhatia was a professor of bioengineering and medicine at the University of California at San Diego from 1998 through 2005. Dr. Bhatia also is an investigator for the Howard Hughes Medical Institute, a member of the Department of Medicine at Brigham and Women's Hospital, a member of the Broad Institute and a member of the Koch Institute for Integrative Cancer Research. Dr. Bhatia holds a Sc.B. in biomedical engineering from Brown University, an S.M. and Ph.D. in Mechanical Engineering from the Massachusetts Institute of Technology and an M.D. from Harvard Medical School.

Dr. Garber has been a member of our Board of Directors since June 2017. He is Provost of Harvard University and the Mallinckrodt Professor of Health Care Policy at Harvard Medical School, a Professor of Economics in the Faculty of Arts and Sciences, Professor of Public Policy in the Harvard Kennedy School of Government, and Professor in the Department of Health Policy and Management in the Harvard T.H. Chan School of Public Health. From 1998 until he joined Harvard in 2011, he was the Henry J. Kaiser Jr. Professor, a Professor of Medicine, and a Professor (by

courtesy) of Economics, Health Research and Policy, and of Economics in the Graduate School of Business at Stanford University. Dr. Garber is a member of the National Academy of Medicine, the American Society of Clinical Investigation, the Association of American Physicians, and the American Academy for Arts and Sciences. He is a Fellow of the American Association for the Advancement of Science, the American College of Physicians, and the Royal College of Physicians. Dr. Garber is also a

Research Associate with the National Bureau of Economic Research and served as founding Director of its Health Care Program for nineteen years. He also has served as a member of the National Advisory Council on Aging at the National Institutes of Health, as a member of the Board of Health Advisers of the Congressional Budget Office and as Chair of the Medicare Evidence Development and Coverage Advisory Committee at the Centers for Medicare and Medicaid Services. Dr. Garber has been a member of the Board of Directors of Exelixis, Inc., a biopharmaceutical company, since 2005. Dr. Garber holds an A.B. summa cum laude, an A.M. and a Ph.D., all in Economics, from Harvard University, and an M.D. with research honors from Stanford University.

Mr. Kearney has been a member of our Board of Directors since May 2011. Mr. Kearney served as the Chief Operating Officer of Hospira, Inc., a specialty pharmaceutical and medication delivery company, from April 2006 to January 2011. From April 2004 to April 2006, he served as Hospira's Senior Vice President, Finance, and Chief Financial Officer, and he served as Acting Chief Financial Officer through August 2006. Mr. Kearney served as Vice President and Treasurer of Abbott Laboratories from 2001 to April 2004. From 1996 to 2001, Mr. Kearney was Divisional Vice President and Controller for Abbott's International Division. Mr. Kearney serves as a member of the Board of Directors at Acceleron Pharma Inc., a biopharmaceutical company. He served as a member of the Board of Directors of Innovia (formerly known as Theravance, Inc.), a royalty management company, from October 2014 through April 2016, and as member of the Board of Directors of AveXis, Inc., a gene therapy company, from January 2016 until its acquisition in May 2018. Mr. Kearney has been a member of the Board of Directors of Levo Therapeutics, Inc., a biotechnology company focused on developing treatments for Prader-Willi Syndrome, since 2018. He received his B.S. in biology from the University of Illinois and his M.B.A. from the University of Denver.

Mr. Lee has been a member of our Board of Directors since September 2012. Mr. Lee serves as an Executive in Residence (XIR) and Partner of General Catalyst Partners, a venture capital firm, positions he has held since April of 2013. Mr. Lee also serves as the Chief Executive Officer of Allego, Inc. and is Executive Chairman of Clarabridge, Inc. Mr. Lee was the Vice President of IBM's Enterprise Marketing Management Group from November 2010 through January 2013. Mr. Lee co-founded Unica Corporation, a provider of software and services used to automate marketing processes, in 1992, and was Unica's President and/or Chief Executive Officer from 1992 through November 2010, when Unica was acquired by IBM. From 1989 to 1992, Mr. Lee was a senior consultant at Digital Equipment Corporation, a supplier of general computing technology and consulting services. Mr. Lee holds a B.S. and an M.S. in electrical engineering and computer science from the Massachusetts Institute of Technology and an M.B.A. from Babson College.

Ms. McGlynn has been a member of our Board of Directors since May 2011. Ms. McGlynn retired from Merck & Co. in 2009, where she served as President, Vaccines and Infectious Diseases from and as President, Hospital and Specialty Products. During her 26 year career at Merck, she also held various leadership roles in the U.S. and globally in marketing, sales, managed care and business development. Following her retirement, Ms. McGlynn served as the President and Chief Executive Officer of the International AIDS Vaccine Initiative, a global not-for-profit organization whose mission is to ensure the development of safe, effective and accessible HIV vaccines for use throughout the world, from 2011 until 2015. Ms. McGlynn serves as a member of the Board of Directors for Air Products and Chemicals, Inc., a company specializing in gases and chemicals for industrial uses, and Amicus Therapeutics, Inc., a biopharmaceutical company. She is also a member of the National Industrial Advisory Committee at the University at Buffalo School of Pharmacy and Pharmaceutical Sciences. Ms. McGlynn holds a B.S. in Pharmacy and an M.B.A. in Marketing from the State University of New York at Buffalo.

Mr. Sachs has been a member of our Board of Directors since 1998. Mr. Sachs is a General Partner at Charles River Ventures, a venture capital firm he joined in 1999. From 1998 to 1999, he served as Executive Vice President and General Manager of Ascend Communications, Inc. From 1997 until 1998, Mr. Sachs served as President and Chief Executive Officer of Stratus Computer, Inc. From 1995 to 1997, he served as Executive Vice President and General Manager of the Internet Telecom Business Group at Bay Networks, Inc. From 1993 to 1995, he served as President and Chief Executive Officer of Xylogics, Inc. Mr. Sachs holds a B.S.E.E. in electrical engineering from Bucknell University, an M.E.E. in electrical engineering from Cornell University, and an M.B.A. from Northeastern University.

Ms. Ullian has been a member of our Board of Directors since 1997. Ms. Ullian served as President and Chief Executive Officer of Boston Medical Center, a private, not-for-profit, 626-bed, academic medical center with a

community-based focus, from 1996 through January 2010. From 1994 to 1996, she served as President and Chief Executive Officer of Boston University Medical Center Hospital. From 1987 to 1994, Ms. Ullian served as President and Chief Executive Officer of Faulkner Hospital. She also serves as a director of Thermo Fisher Scientific Inc. Ms. Ullian retired from Hologic, Inc.'s Board of Directors in March 2018. Ms. Ullian holds a B.A. in political science from Tufts University and an M.P.H. from the University of Michigan.

Mr. Young has been a member of our Board of Directors since May 2014. Mr. Young is a Senior Advisor with Blackstone Life Sciences (which acquired Clarus Ventures in 2018). Mr. Young joined Clarus Ventures, a life sciences venture capital firm, in 2010. Prior to Clarus Ventures, Mr. Young served from 1999 until June 2009 as the Chairman and Chief Executive Officer of Monogram Biosciences, Inc., a biotechnology company acquired by Laboratory Corporation of America in June 2009. From 1980 to 1999, Mr. Young was employed at Genentech, Inc. in positions of increasing responsibility, including as Chief Operating Officer from 1997 to 1999, where he was responsible for all product development, manufacturing and commercial functions. Prior to joining Genentech, Mr. Young was with Eli Lilly & Co. for 14 years. Mr. Young currently serves as the Chairman of the Board of Directors of NanoString Technologies, Inc., and as a member of the Board of Directors of Theravance BioPharma Inc. Mr. Young retired from BioMarin Pharmaceutical Inc.'s Board of Directors in November 2015 and as Biogen's Chairman of the Board in June 2014. Mr. Young holds a B.S. in Chemical Engineering from Purdue University, an M.B.A. from Indiana University and an Honorary Doctorate in Engineering from Purdue University. Mr. Young was elected to the National Academy of Engineering in 1993 for his contributions to biotechnology.

ITEM 1A. RISK FACTORS

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.

Risks Related to Our Business

All of our product revenues and the vast majority of our total revenues are derived from sales of medicines for the treatment of cystic fibrosis. If we are unable to continue to increase revenues from sales of our cystic fibrosis 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 CF medicines. SYMDEKO/SYMKEVI, ORKAMBI and KALYDECO net product revenues represented approximately 25%, 41% and 33% of our total revenues in the year ended December 31, 2018, respectively. As a result, our future success is dependent on our ability to continue to increase revenues from sales of our CF medicines. In the near term, this will require us to increase CF net product revenues from our current medicines and in the longer term, this will require us to successfully develop, obtain approval for and commercialize at least one triple combination therapy that will allow us to treat F508del/Min patients and to improve the treatment options available to patients with CF who are eligible for our current medicines.

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

- that one or more competing therapies may successfully be developed as a treatment for patients with CF;
- that we may experience adverse developments with respect to development or commercialization of our CF medicines and/or CF drug candidates; and
- 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.

If one or more 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 stock price would likely decline.

We are investing significant resources in the development of our next-generation CFTR corrector compounds in triple combinations and if we are unable to show the safety and efficacy of these regimens, experience delays in doing so or are unable to successfully commercialize at least one of these medicines, our business would be materially harmed.

We are investing significant resources in the development of our next-generation CFTR corrector compounds, VX-659 and VX-445, which are currently being evaluated in Phase 3 clinical development as part of separate triple combination treatment regimens for patients with CF. We believe that a significant portion of the long-term value attributed to our company by investors is based on the commercial potential of these triple combination therapies. While we believe, based on data, including interim data, from the ongoing VX-659 Phase 3 clinical trials and the status of the ongoing VX-445 clinical trials, that we will be able to submit an NDA to the FDA for a triple combination regimen no later than mid-2019, there can be no assurances that the data will be sufficient to submit an NDA on this timeline, or at all.

Clinical trial data are subject to differing interpretations and, even if we view data as sufficient to support the safety, effectiveness and/or approval of a triple combination regimen, regulatory authorities may disagree and may require additional data, may limit the scope of the approval or may deny approval altogether. Furthermore, interim results of a clinical trial may differ materially from final results from such clinical trials. If the final data from our ongoing Phase 3 clinical trials are not favorable, the FDA and comparable foreign regulatory authorities may not approve these treatment regimens and/or we may be forced to delay or terminate the development of these treatment regimens, which would have an adverse effect on our business. Even successfully completed large-scale clinical trials may not result in marketable medicines. If a triple combination fails to achieve its primary endpoint in clinical trials, if safety issues arise, or if the results from our clinical trials are otherwise inadequate to support regulatory approval of our triple combination therapies, commercialization of that combination regimen could be delayed or halted.

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Even if we gain marketing approval for one or more combination therapies containing a next-generation CFTR corrector compound in a timely manner, we cannot be sure that such combination therapy will be commercially successful. In addition, since we expect that a significant portion of the patients for whom a triple combination treatment regimen would be indicated would also be eligible for our then-existing medicines, a portion of the revenues from our triple combination regimens will likely displace revenues from our then-marketed products, reducing the overall positive effect of the commercialization of our triple combination regimens on our total revenues.

If the anticipated or actual timing of marketing approvals for these triple combination regimens, or the market acceptance of these triple combination regimens, if approved, including treatment reimbursement levels agreed to by third-party payors, do not meet the expectations of investors or public market analysts, the market price of our common stock would likely decline.

We have experienced challenges commercializing products outside of the United States, 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 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 period of time and reimbursement decisions are made on a country-by-country 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 medicines given the relative higher cost of these products as compared to other types of pharmaceutical products - and countries are increasingly refusing to reimburse costly medicines. As a result, we have recognized limited ex-U.S. net product revenues for ORKAMBI in various countries outside the United States, including the United Kingdom and France, both of which represent significant potential markets for ORKAMBI. Our future product revenues, including from ORKAMBI, SYMKEVI and our triple combination regimens, if approved, 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 United States 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.

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

A number of companies are seeking to identify and develop drug candidates for the treatment of CF, including AbbVie, Eloxx Pharmaceuticals, ProQR Therapeutics, Proteostasis Therapeutics, Translate Bio, and several private companies. Our competitors have research and development programs directed at identifying CFTR potentiators, CFTR correctors, ENaC inhibitors and drug candidates with other mechanisms of action or that utilize new therapeutic approaches that seek to address the underlying cause of CF. Our success in rapidly developing and commercializing our CF products may increase the resources that our competitors allocate to the development of these potential treatments for CF. Our competitors are exploring the development of drug candidates both as monotherapies and as part of combination regimens. If one or more competing therapies are successfully developed as a treatment for patients with CF, our products and our CF net product revenues could face competitive pressures. If one or more competing therapies prove to be superior to our then existing products and/or drug candidates for the treatment of CF, our business would be materially adversely affected.

In addition, our business faces competition from major pharmaceutical companies, such as Abbvie, Bristol-Myers Squibb, Gilead, Johnson & Johnson, Merck, Novartis, Pfizer, Sanofi and Roche, which possess substantially greater financial resources than we possess, and 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. As an example of how competition has affected our business in the past, in 2013 and 2014 we experienced a rapid decline in the number of patients being treated with INCIVEK, a product we

previously marketed for the treatment of hepatitis C virus infection, as a result of competition from a treatment regimen identified by a small biotechnology company and developed and commercialized by Gilead.

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 drugs 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 as well as our most advanced drug candidates are related to the treatment of patients with CF. There are many other companies developing drugs for the same indications 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 drugs.

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. Drugs 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 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 commercial products and our triple combination treatment regimens contain ivacaftor or VX-561, a deuterated version of ivacaftor. As a result, if any of our products or drug candidates were to experience safety issues, our other commercial products as well as one or more of our drug candidates, 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.

In addition, 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 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 drugs, or if patients do not remain on treatment or comply with the prescribed dosing regimen, our product revenues would be materially harmed in future periods.

Our drugs may not gain or maintain market acceptance among physicians and patients. Effectively marketing our drugs and any of our drug candidates, if approved, requires substantial efforts, both prior to launch and after approval. Physicians may elect not to prescribe our drugs, and patients may elect not to take them or may discontinue use of our drugs 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 drug;
- convenience and ease of administration;
- other potential advantages of alternative treatment methods; and
- ineffective sales, marketing and/or distribution support.

If our drugs 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.

Our sales of 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 United States and the national health care systems in many international 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 such government authorities are increasingly attempting to limit or regulate the price of drug products. In the United States, 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 through various other actions. In reimbursement negotiations, many payers are demanding price discounts 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, international government payers also are requiring companies to establish product “cost-effectiveness” as a condition of reimbursement. These cost-effectiveness reviews frequently are subjective, may not account for many of the benefits provided by innovative medicines, and have led to conclusions that certain medicines, including our products in certain jurisdictions, are not worth their price. As a result, certain countries have declined to reimburse some of our products. Although not mandated in the United States, various organizations have started advocating for cost-effectiveness analyses in the United States as well. Notably, if U.S. payors were to adopt such assessments and make corresponding (negative) coverage determinations, we could expect to see a decrease in our future net product revenues, which could harm our business.

There is also an increase in laws, regulations, and activity related to drug pricing and drug pricing transparency. In the United States, various states, including Nevada, Maryland, Louisiana, New York, California, and Oregon, have passed legislation requiring companies to disclose significant amounts of information, including information relating to drug prices, drug price increases, and spending on research, development, and marketing. Although it is not clear what states ultimately will do with the information collected, some laws were designed to obtain additional product discounts, and we likely will continue to see more state action, which could require further disclosures or other actions.

Complying with these laws requires significant personnel and operational resources and deters focus on our business. 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.

In addition, in the United States and some foreign jurisdictions, there have been a number of legislative and regulatory proposals and initiatives to change the health care system in ways that could affect our ability to sell products. For example, in the United States, there have been ongoing federal legislative and administrative efforts as well as legal challenges seeking to repeal, substantially modify or invalidate some or all of the provisions of the ACA. Tax legislation enacted at the end of 2017 eliminated the tax penalty for individuals who do not maintain sufficient health insurance coverage beginning in 2019. The Bipartisan Budget Act of 2018 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% starting in 2019. As a result, there is uncertainty regarding future changes in the laws and regulations applicable to the health

care system and the effect any such changes may have on our business. Some of these proposed and implemented reforms have resulted, or could result, in reduced reimbursement rates and/or more limited access for our current or future products, which would adversely affect our business, operations and financial results.

The increasing availability and use of innovative specialty pharmaceuticals, combined with their relative higher cost as compared to other types of pharmaceutical products, is beginning to generate 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 limit the prices that can be charged for our products and may limit our commercial opportunity. The increasing use of health technology assessments in markets around the world and the financial challenges faced by many governments may lead to significant adverse effects on our business.

Any legislation or regulatory changes or relaxation of laws that restrict imports of drugs from other countries, revisions to reimbursement or pharmaceuticals under government programs or general budget control actions also could reduce the net price we receive for our products.

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 federal False Claims Act and the anti-kickback provisions of the federal Social Security Act, laws prohibiting off-label product promotion and other similar laws and regulations both in United States and in non-U.S. markets. While we have a corporate compliance program 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.

The federal anti-kickback law 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. The federal statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, patients, purchasers and formulary managers on the other hand, and therefore constrains our marketing practices and our various service arrangements with physicians, including physicians who make clinical decisions to use our products. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution, the exemptions and safe harbors are drawn narrowly and have been interpreted by courts as such.

Federal false claims laws 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 non-covered 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.

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 CF patients 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 patients represent only a portion of the total patients 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 letter, injunction, seizure, civil fine 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 recent years, legislation has been adopted at the federal, state and local level requiring pharmaceutical companies to establish marketing compliance programs, file periodic reports or make periodic public disclosures on sales, marketing, pricing, clinical trials, health care provider payments and other activities. For example, as part of the ACA,

the federal government enacted the Open Payments (referred to as the Sunshine Act) provisions. Open Payments requires pharmaceutical manufacturers to report annually to the Centers for Medicare and Medicaid Services 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 now have similar reporting obligations

throughout the European Union, or 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 would result in significant civil monetary penalties.

The sales and marketing practices of our industry have been the subject of increased scrutiny from governmental entities in the United Sates and other countries in which we market our products, and we believe that this trend will continue. The risk of our being found in violation of these laws is increased by the fact that many of them have not been fully interpreted by the regulatory authorities or the courts, and their provisions are subject to a variety of interpretations. If our past or present operations are found to be in violation of any such laws or any other governmental regulations that may apply to us, 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. Any action against us for violation of these laws, even if we successfully defend against them, also could cause us to incur significant legal expenses and divert our management's attention from the operation of our business.

There is also enhanced scrutiny of company-sponsored patient assistance programs, including insurance premium and co-pay assistance programs and donations to third party charities that provide such assistance. If we, or our vendors or donation recipients are deemed to fail to comply with relevant laws, regulations or government guidance in the operation of these programs, we could be subject to significant fines and 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 which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

We participate in the Medicaid Drug Rebate Program and a number of other federal and state government pricing programs in the U.S. in order to obtain coverage for the product by certain government health care programs. These programs would generally require us to pay rebates or provide discounts to certain private purchasers or government payers 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. We may also 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. Responding to current and future changes 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.

Changes in laws and regulations governing the privacy and protection of data and personal information could adversely affect our business.

We are subject to data privacy and protection laws and regulations that apply to the collection, transmission, storage and use of proprietary information and personally-identifying information, which among other things, impose certain requirements relating to the privacy, security and transmission of individually identifiable health information. 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. Various foreign countries also have, or are developing, laws governing the collection, use, disclosure, security, and cross-border transmission 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 went into effect in May 2018 and has imposed new obligations on us with respect to our processing of personal data and the cross-border transfer of such data. While we continue to address the implications of the recent changes to E.U. 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 and our

efforts to comply with the evolving data protection rules may be unsuccessful. We must devote significant resources to understanding and complying with this changing landscape. Failure to comply with laws regarding data protection would expose us to risk of enforcement actions taken by data protection authorities in the E.U. and the potential for significant penalties if we are found to be non-compliant. Similarly, failure to comply with federal and state laws in the United States regarding privacy and security of personal information could expose us to penalties under such laws. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our business.

The EMA has adopted a policy on publication of clinical data whereby it will publish clinical reports submitted as part of MAAs for drugs. The EMA aims to publish reports within 60 days after a decision on the application has been made by the European Commission. The ability of third-parties to review and/or analyze the raw data from our clinical trials may increase the risk of patient confidentiality breaches and could result in enhanced scrutiny of our clinical trials results. Such scrutiny could result in misconceptions being spread about our drugs and drug candidates, even if the underlying analysis of such review turns out to be flawed. These publications could also result in the disclosure of information to our competitors that we might otherwise deem confidential, which could harm our competitive position.

The use of social media platforms presents risks and challenges.

Social media is being used by third parties to communicate about our products and drug 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 drug or a drug candidate, which could result in reporting obligations. In addition, our employees may engage on social media in ways that may not comply with our social media policy or 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. If any of these events were to occur or we otherwise fail to comply with applicable regulations, we could incur liability, face restrictive regulatory actions or incur other harm to our business, including damage to our reputation.

Risks Related to Development, Clinical Testing and Regulation of Our Products and Drug Candidates

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

Our business depends upon the successful development and commercialization of drug candidates. These drug 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 drug candidates. Discovery and development efforts for new pharmaceutical products, including new combination therapies, are resource-intensive and may take 10 to 15 years or longer for each drug candidate. Despite our efforts, our drug 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 candidate;
- 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 products.

We have recently completed and/or have ongoing or planned clinical trials for several of our drug candidates. The strength of our company's product portfolio and pipeline will depend in large part upon the outcomes of these clinical trials and our ability to develop and commercialize combination treatments for CF, including our next-generation CFTR corrector compounds and develop treatments for other diseases. 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 drug candidate or program. For example, in 2018 we discontinued development of VX-210 based on a recommendation by the data Safety Monitoring Board, or DSMB, to stop a clinical trial early due to futility.

Moreover, clinical data are often susceptible to varying interpretations, and many companies that have believed their drug candidates performed satisfactorily in clinical trials have nonetheless failed to obtain marketing approval of their

drug 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 drug candidate.

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. Accordingly, the results from completed preclinical studies and clinical trials may not be replicated in later clinical trials, and ongoing clinical trials for our drug candidates may not be predictive of the results we may obtain in later-stage clinical trials or of the likelihood of approval of a drug candidate for commercial sale. In addition, from time to time we report interim data from our clinical trials. Interim data from a clinical trial may not be predictive of final results from the clinical trial.

If we are unable to obtain regulatory approval, we will be unable to commercialize our drug 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 and/or Breakthrough Therapy designation for some of our drug candidates. Drug candidates that receive one or both 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 drug candidates meets the criteria for Fast Track and/or Breakthrough Therapy designation, the FDA may disagree and instead determine not to make such designation. The receipt of one or both of these designations for a drug candidate does not guarantee a faster development process, review or approval compared to drugs 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 drugs or drug candidates qualifies for Fast Track and/or Breakthrough Therapy designation, the FDA may later decide to withdraw such designation if it determines that the drug or drug candidate no longer meets the conditions for qualification.

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

If clinical trials are prolonged or delayed, our development timelines for the affected development program could be extended, our costs to develop the drug candidate could increase and the competitive position of the drug 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;
- 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 inconclusive results, unforeseen complications in testing or clinical investigator error;
- inadequate supply or deficient quality of drug 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 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 drug candidates with similar mechanisms of action or structures to drug candidates that we are developing;
- favorable results in testing of our competitors' drug candidates, or FDA or foreign regulatory authority approval of our competitors' drug 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.

Our ability to enroll patients in our clinical trials in sufficient numbers and on a timely basis is subject to a number of factors, including the size of the patient population, the nature of the protocol, the proximity of patients to clinical sites, the availability of effective treatments for the relevant disease, the number of other clinical trials ongoing and competing for patients in the same indication and the eligibility criteria for the clinical trial. In addition, patients may drop out of our clinical trials or may be lost to follow-up medical evaluation after treatment ends, and this could impair the validity or statistical significance of the trials. Delays in patient enrollment or unforeseen drop-out rates may result in increased costs and longer development times.

We, our collaborators, the FDA or other applicable regulatory authorities may suspend clinical trials of a drug 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 drug candidate and our business.

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 drug candidates.

We have a number of regulated processes and systems that are required both prior to and following approval of our drugs and drug 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 drug 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.

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Risks Related to Collaborations and other Business Development Activities

Our ability to execute on our long-term strategy depends in part on our ability to acquire rights to additional drugs, drug candidates and other technologies that have the potential to add to our pipeline or provide us with new commercial opportunities.

In order to achieve our long-term business objectives, our strategy is to supplement our internal pipeline by acquiring rights to additional drugs, drug candidates and other technologies that have the potential to provide us with new commercial opportunities, including in CF and in therapeutic areas outside of CF. We may not be able to acquire, in-license or otherwise obtain rights to additional drugs, drug candidates or other technologies on acceptable terms or at all. We have faced and will continue to face significant competition for the acquisition of rights to these types of drugs, drug candidates and other technologies from a variety of other companies with interests in the specialty pharmaceutical marketplace, 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 drugs, drug candidates or technologies, which may provide incentives for companies to advance these drugs, drug candidates or technologies independently. Because of these competitive pressures, the cost of acquiring, in-licensing or otherwise obtaining rights to such drugs, drug 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. This competition is most intense for approved drugs and late-stage drug candidates, which have the lowest risk and would have the most immediate effect on our financial performance.

We may not realize the anticipated benefits of potential acquisitions or licenses to businesses, drugs, drug candidates and other technologies, and the integration following any such acquisition or license may disrupt our business and management.

We may acquire a business or the rights to drugs, drug candidates or other technologies. In recent years we have entered into both acquisition and collaboration arrangements, including our acquisition of VX-561 from Concert, our agreement with 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 and our collaboration agreement with Moderna, pursuant to which we are seeking to identify and develop mRNA therapeutics for the treatment of CF. With respect to each of these transactions and any additional acquisition of a business or rights to drugs, drug candidates or other technologies, we may not realize the anticipated benefits of such transaction, each of which involves numerous risks. These risks include:

- failure to successfully develop and commercialize the drugs, drug candidates or technologies that we acquire or license or to achieve other strategic objectives;
- inadequate or unfavorable data from clinical trials evaluating the acquired or licensed drug or drug candidates;
- entry into markets in which we have no or limited direct prior experience or where competitors in such markets have stronger market positions;
- disruption of our ongoing business and distraction of our management and employees from other opportunities and challenges;
- potential failure of the due diligence processes to identify significant problems, liabilities or other shortcomings or challenges of an acquired company, or acquired or licensed drug, drug candidate or technology, including but not limited to, problems, liabilities or other shortcomings or challenges with respect to intellectual property, product quality, safety, accounting practices, employee, customer 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;
- difficulty in integrating the drugs, drug candidates, technologies, business operations and personnel of an acquired asset or company; 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 and licensing arrangements are inherently risky, and ultimately, if we do not complete an announced acquisition or license transaction or integrate an acquired business, or an acquired or licensed drug, drug candidate or other technology successfully and in a timely manner, we may not realize the benefits of the acquisition or license to the extent anticipated and the perception of the effectiveness of our management team and our company may suffer in the marketplace. Additionally, we may later incur impairment charges related to assets acquired in any such transaction. For example, we entered into a strategic collaboration and license agreement with Parion Sciences, Inc., or Parion, to develop ENaC inhibitors in 2015 and incurred an impairment charge related to this collaboration in the third quarter of 2017. In addition, even if we achieve the long-term benefits associated with strategic transactions, our expenses and short-term costs may increase materially and adversely affect our liquidity and short-term net income (loss). Future licenses or acquisitions could result in potentially dilutive issuances of equity securities, the incurrence of debt, the creation of contingent liabilities, impairment expenses related to goodwill, and impairment or amortization expenses related to other intangible assets, 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 drug candidates.

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

- Our collaborators may change the focus of their development and commercialization efforts or may have insufficient resources to effectively develop our drug candidates. The ability of some of our products and drug candidates to reach their potential could be limited if collaborators decrease or fail to increase development or commercialization efforts related to those products or drug candidates. Our collaboration agreements 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.
- Any future 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 drugs or drug 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 drug candidates, might lead to additional responsibilities for us with respect to drug candidates, or might result in litigation or arbitration. Any such disagreements would divert management attention and resources and 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.

Additionally, if a collaborator were to be involved in a business combination, it might deemphasize or terminate the development or commercialization of any drug 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 drug 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 early-stage clinical development programs, some of which are being developed in collaboration with a third party. For example, we have an ongoing collaboration with Janssen, pursuant to which Janssen is developing drug candidates that resulted from our research activities. At any time, we may determine that in order to continue development of a drug candidate or program or successfully commercialize a drug we need to identify a collaborator or amend or expand an existing collaboration. 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 or similar regulatory authorities outside the United States, the potential market for the subject drug candidate, the costs and complexities of manufacturing and delivering such drug 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 Third-Party Manufacturing and Reliance on Third Parties

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

We rely on a worldwide network of third-party manufacturers to manufacture our drugs for commercial use and our drug candidates for clinical trials. As a result of our reliance on these third-party manufacturers and suppliers, we could be subject to significant supply disruptions outside of our control. Our supply chain for sourcing raw materials and manufacturing drug product ready for distribution 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. Establishing and managing this global supply chain requires a significant financial commitment and the creation and maintenance of numerous third-party contractual relationships. Although we attempt to manage the business relationships with companies in our supply chain, we do not have control over their operations. 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 or any other performance failure by any third-party manufacturer on which we rely. Any supply disruptions could disrupt sales of our products and/or the timing of our clinical trials.

We require a supply for our medicines for commercial sale and a supply of our drug candidates for use in our clinical trials. While we have developed some internal capabilities, a majority of the manufacturing steps needed to produce our drug candidates and drug products are performed through a third-party manufacturing network. To ensure the stability of our supply chains we aim to develop additional sources of manufacture for all steps of our manufacturing processes at the time of, or shortly after, marketing approval. Therefore, at any point in time, we may have a limited number of single source manufacturers for certain steps in our manufacturing processes, particularly for recently launched products.

If we or our third-party manufacturers become unable or unwilling to continue manufacturing product on our behalf 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 drug products could delay the completion of clinical trials and affect timelines for regulatory filings. There can be no assurance that we will be able to establish and maintain secondary manufacturers for all of our drug candidates and drug 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 drug 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 drug candidates manufactured by other suppliers utilizing the same process.

We rely on third parties to conduct certain pre-clinical work and clinical trials, 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 contract research organizations 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. 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. 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 these activities, it may result in a delay of the affected clinical trial or drug development program. 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 drug candidates could be delayed.

Risks Related to Intellectual Property

If our patents do not protect our drugs or our drugs 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 have numerous issued patents and pending patent applications in the United States, 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 drugs, 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 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, includes a number of significant changes to United States patent law. These include provisions that affect the way patent applications are prosecuted and may also affect patent litigation. The United States Patent Office developed new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, became effective in March 2013. 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 drug candidates or their use. If a third party also has filed a U.S. patent application relating to our drugs or drug 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 Lahey-Smith Act, if a third-party has an earlier filed U.S. patent application relating to our drugs or drug 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, resulting 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 might not contain claims that are sufficiently broad to prevent others from utilizing our technologies. For instance, the issued patents relating to our drugs or drug candidates may be limited to a particular molecule or molecules and may not cover similar molecules that have similar clinical properties. Consequently, our competitors may

independently develop competing products that do not infringe our patents or other intellectual property. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future products.

The laws of many foreign jurisdictions do not protect intellectual property rights to the same extent as in the United States 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 drug candidates, it is possible that a patent may expire before a drug candidate can be commercialized, or a patent may expire or remain in effect for only a short period following commercialization of such drug candidate. This would result in a minimal or non-existent period of patent exclusivity. If our drug candidates are not commercialized significantly ahead of the expiration date of any applicable patent, or if we have no patent protection on such drug 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, which is inherently costly and unpredictable.

There is considerable uncertainty within our industry about the validity, scope and enforceability of many issued patents in the United States 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 drugs or to remove our drugs 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 financial statements.

To the extent that valid present or future third-party patents or other intellectual property rights cover our drugs, drug 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 drugs. 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 as well as patient-level clinical trial data. New laws in the E.U. also have expanded protections related to personal data and provided for increased sanctions for violations. Collectively, our expansion and these new requirements are adding to our compliance costs and expose us to potential sanctions for failing to meet the enhanced safeguards and reporting demands 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. 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 conducting operations in foreign countries 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;
- collectibility 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 are interpreted and enforced differently across jurisdictions and 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 United States;
- import and export licensing requirements, tariffs, and other trade and travel restrictions;
- 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 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.

Risk relating to the Referendum of the United Kingdom's Membership of the European Union.

Our European headquarters and European research facility are located in the United Kingdom, or the U.K., and a significant portion of our ex-U.S. net product revenues are derived from sales in the U.K. In June 2016, the U.K. held a referendum in which voters approved an exit from the E.U., commonly referred to as "Brexit." The U.K. government provided official notice of withdrawal from the E.U. in March 2017 and has a period of two years from the date of its formal notification (such period ending March 29, 2019) to negotiate the terms of its withdrawal from, and future relationship with, the E.U., including the terms of trade between the U.K. and the E.U. and potentially other countries. If no formal withdrawal agreement is reached, then it is expected that the U.K.'s membership in the E.U. will automatically terminate two years after the submission of the notification of the U.K.'s intention to withdraw from the E.U., unless all remaining member states unanimously consent to an extension of this period. Discussions between the U.K. and the E.U. focused on finalizing withdrawal issues and transition agreements are ongoing. However, limited progress to date in these negotiations and ongoing uncertainty within the U.K. government increases the possibility of the U.K. leaving the E.U. on March 29, 2019 without a withdrawal agreement and associated transition period in place, which is likely to cause significant market and economic disruption, which may cause third-party payors, including governmental organizations, to closely monitor their costs and reduce their spending budgets. The effects of Brexit will depend on any agreements the U.K. makes to retain access to E.U. markets either during a transitional period or more permanently. 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. If we do not obtain appropriate levels of insurance, any potential claims could adversely affect our business.

We are or may be involved in various legal proceedings, including securities class action lawsuits and claims related to product liability, intellectual property and breach of contract. Such proceedings may involve claims for, or the possibility of, 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 drug 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. The size and complexity of our information technology and information security systems makes such systems potentially vulnerable to service interruptions or to security breaches. 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 in an attempt 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, cyber-attacks are increasing in their frequency, sophistication and intensity, and have become increasingly difficult to detect. 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.

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

Because our drug discovery and development activities are highly technical in nature, 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 compensation-related 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 — such as options and restricted stock units — is significantly affected by movements in our stock price, 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. 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 have increased competition for the available pool of skilled employees, especially in technical fields, and the high cost of living in Massachusetts makes it difficult to attract employees from other parts of the country to Massachusetts. 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 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.

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.

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 would have a material adverse effect on our business.

Risks Related to Holding Our Common Stock

Our stock price may fluctuate.

Market prices for securities of companies such as ours are highly volatile. From January 1, 2018 to December 31, 2018, our common stock traded between $144.07 and $194.92 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 our net product revenues and operating expenses for completed periods and guidance regarding future periods;
- announcements of FDA actions with respect to our drugs or our competitors' drugs, or regulatory filings for our drug candidates or those of our competitors, or announcements of interim or final results of clinical trials or nonclinical studies relating to our drugs, drug candidates or those of our competitors;
- developments in domestic and international governmental policy or regulation, for example, relating to drug pricing or intellectual property rights;
- 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.

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 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 level 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 drug candidates or competitive products or potentially competitive drug 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 drug candidates, competitive products or potentially competitive drug 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.

Changes in tax laws, regulations and treaties could affect our future taxable income.

A change in tax laws, treaties or regulations, or their interpretation, of any country in which we operate could materially affect us if we generate taxable income in a future period. On December 22, 2017, the United States enacted H.R.1., known as the Tax Cuts and Jobs Act, which represented a substantial change to tax laws in the United States, but which did not have a material impact on our financial statements because we maintained a valuation allowance on the majority of our net operating losses and other deferred tax assets as of December 31, 2017, which was only released at the end of 2018. However, over the next several years we expect to utilize our net operating losses and other deferred assets, and any future changes in tax laws could have a material effect on our business. We continue to 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.

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. Additionally, our pledge of specified assets as collateral to secure our obligations under our credit agreement may limit our ability to obtain additional debt financing. 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, drugs or drug 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 agreement impose restrictions on our business, reducing our operational flexibility and creating default risks.

In October 2016, we entered into a credit agreement providing for a $500 million revolving facility, $300 million of which was drawn at closing and subsequently paid off in February 2017. The credit agreement provides that, subject to the

satisfaction of certain conditions, we may request that the borrowing capacity under the credit agreement be increased by an additional $300.0 million. All outstanding borrowings under the credit agreement mature on October 13, 2021. 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 agreement requires that we comply with certain financial covenants, including (i) a consolidated leverage ratio covenant and (ii) a consolidated EBITDA covenant, in each case to be measured on a quarterly basis. Further, the credit agreement includes 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 agreement and/or our capital leases and could have a material adverse effect on our business. Additionally, our obligations under the credit agreement are unconditionally guaranteed by certain of our domestic subsidiaries. All obligations under the credit agreement, and the guarantees of those obligations, are secured by substantially all of our assets and the assets of all guarantors (excluding intellectual property, owned and leased real property and certain other excluded property), including the pledge of all or a portion of the equity interests of certain of our subsidiaries. If we fail to satisfy our obligations under the credit agreement or are unable to obtain sufficient funds to make payments, the lenders could foreclose on our pledged collateral.

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

As of December 31, 2018, we had 255.2 million shares of common stock issued and outstanding. As of December 31, 2018, we also had outstanding options to purchase 8.6 million shares of common stock with a weighted-average exercise price of $111.46 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 options and restricted stock units 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.

Our Board of Directors has authorized a share repurchase program of up to $500 million to repurchase shares of our common stock. 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. Although we amended our charter to eliminate staggered terms for our Board of Directors, our shareholders will not have the ability to vote for all members of the Board of Directors on an annual basis until 2020. 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 and, in particular, the description of our Business set forth in Item 1, the Risk Factors set forth in this Item 1A and our Management's Discussion and Analysis of Financial Condition and Results of Operations set forth in Item 7 contain or incorporate a number of forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, including statements regarding:

- our expectations regarding the amount of, timing of and trends with respect to our revenues, costs and expenses and other gains and losses, including those related to our CF net product revenues;
- our expectations regarding clinical trials, development timelines and regulatory authority filings and submissions for ivacaftor, lumacaftor, tezacaftor, VX-659, VX-445, VX-150 and the timelines for regulatory filings for a triple combination regimen;
- our ability to obtain reimbursement for our medicines in ex-U.S. markets and our ability to otherwise successfully market our medicines or any drug candidates for which we obtain regulatory approval;
- our expectations regarding the timing and structure of clinical trials of our drugs and drug candidates and the expected timing of our receipt of data from our ongoing and planned clinical trials;
- 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 drug candidates for further investigation, clinical trials or potential use as a treatment;
- our plan to continue investing in our research and development programs and our strategy to develop our drug candidates, alone or with third party-collaborators;
- the establishment, development and maintenance of collaborative relationships;
- potential business development activities;
- potential fluctuations in foreign currency exchange rates;
- our ability to use our research programs to identify and develop new drug candidates to address serious diseases and significant unmet medical needs; and
- our liquidity and our expectations regarding the possibility of raising additional capital.

Any or all of our forward-looking statements in this Annual Report on Form 10-K may turn out to be wrong. They can be affected by inaccurate assumptions or by known or unknown risks and uncertainties. Many factors mentioned in this Annual Report on Form 10-K will be important in determining future results. Consequently, no forward-looking statement can be guaranteed. Actual future results may vary materially from expected results. We also provide a cautionary discussion of risks and uncertainties under "Risk Factors" above in this Item 1A. These are factors and uncertainties that we think could cause our actual results to differ materially from expected results. Other factors and uncertainties besides those listed there could also adversely affect us.

Without limiting the foregoing, the words "believes," "anticipates," "plans," "intends," "expects" and similar expressions are intended to identify forward-looking statements. There are a number of factors and uncertainties that could cause actual events or results to differ materially from those indicated by such forward-looking statements, many of which are beyond our control, including the factors and uncertainties set forth under "Risk Factors" above in this Item 1A. In addition, the forward-looking statements contained herein represent our estimate only as of the date of this filing and should not be relied upon as representing our estimate as of any subsequent date. While we may elect to update these forward-looking statements at some point in the future, we specifically disclaim any obligation to do so to reflect actual results, changes in assumptions or changes in other factors affecting such forward-looking 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, 2018 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. The leases commenced in December 2013 and will extend until December 2028. We have an option to extend the term of the leases for an additional ten years. In addition, we have a lease for approximately 100,000 square feet of space in the Boston Marine Industrial Park, in close proximity to our corporate headquarters. We are using this additional space for certain logistical and laboratory operations and manufacturing equipment that complement the office and laboratory facilities at our corporate headquarters.

Additional United States and Worldwide Locations

In addition to our facilities in Massachusetts, we lease an aggregate of approximately 300,000 square feet of space. We lease approximately 170,000 square feet of office and laboratory space in San Diego, California to a lease that expires in 2035. Our other facilities include laboratory and office space to support our research and development organizations Milton Park, Abingdon, England, and office space in many of the countries in which we sell our products.

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, 2019, there were 1,277 holders of record of our common stock.

Performance Graph

We became part of the Standard & Poor's 500 ("S&P 500®") Stock Index in 2013.

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

We have a share repurchase program, announced in January 2018, under which we are authorized to repurchase up to $500.0 million of our common stock by December 31, 2019. As of September 30, 2018, we had repurchased $211.0 million of common stock under this program and had remaining available $289.0 million to repurchase additional shares under this program. The table set forth below shows repurchases of securities by us during the three months ended December 31, 2018, including shares repurchased under our share repurchase program and a small number of restricted shares repurchased by us from employees pursuant to our equity programs. As of December 31, 2018, we had repurchased $350.0 million of common stock under the share repurchase program and had remaining available $150.0 million to repurchase additional shares pursuant to this program.

Period	Total Number of Shares Purchased (1)	Average Price Paid per Share	Total Number of Shares Purchased as Part of Publicly Announced Plans or Programs (2)	Maximum Number of Shares (or approximate dollar amount) that May Yet be Purchased Under the Plans or Programs (2)
Oct. 1, 2018 to Oct. 31, 2018	278,920	$174.24	275,351	$240,390,554
Nov. 1, 2018 to Nov. 30, 2018	346,159	$165.80	338,979	$182,995,963
Dec. 1, 2018 to Dec. 31, 2018	197,930	$166.70	196,878	$150,000,059
Total	823,009	$168.88	811,208	$150,000,059

(1) Consists of 811,208 shares repurchased pursuant to our share repurchase program (described in footnote 2 below) at an average price of $171.33 per share and 11,801 restricted shares repurchased for $0.01 per share from our employees pursuant to our equity plans. While we have restricted shares that are continuing to vest under our equity plans that are subject to repurchase rights upon termination of service, we have transitioned our equity program to granting restricted stock units. Unvested restricted stock units are forfeited upon termination of service and do not result in an issuer repurchase that would be reflected in this table.

(2) Our board of directors has approved a share repurchase program pursuant to which we are authorized to repurchase up to $500.0 million of our common stock by December 31, 2019; the program was announced on January 31, 2018. Under the share repurchase program, we are authorized to purchase shares from time to time through open market or privately negotiated transactions and 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.

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ITEM 6. SELECTED FINANCIAL DATA

The following unaudited selected consolidated financial data are derived from our audited consolidated financial statements. These data should be read in conjunction with our audited consolidated financial statements and related notes that are included elsewhere in this Annual Report on Form 10-K and with "Management's Discussion and Analysis of Financial Condition and Results of Operations" included in Item 7.

	Year Ended December 31,				
	2018	2017	2016	2015	2014
Consolidated Statements of Operations Data:	(in thousands, except per share amounts)				
Product revenues, net	$3,038,325	$2,165,480	$1,683,632	$1,000,324	$487,821
Collaborative and royalty revenues (1)	9,272	323,172	18,545	32,012	92,594
Total revenues	3,047,597	2,488,652	1,702,177	1,032,336	580,415
Total costs and expenses (2)	2,412,447	2,365,409	1,692,241	1,499,215	1,272,827
(Benefit from) provision for income taxes (3)	(1,486,862)	(107,324)	16,665	30,381	6,958
Net income (loss) attributable to Vertex	$2,096,896	$263,484	$(112,052)	$(556,334)	$(738,555)
Diluted income (loss) from continuing operations per share attributable to Vertex common shareholders	$8.09	$1.04	$(0.46)	$(2.31)	$(3.14)
Shares used in per diluted share calculations	259,185	253,225	244,685	241,312	235,307

	As of December 31,				
	2018	2017	2016	2015	2014
Consolidated Balance Sheet Data:	(in thousands)				
Cash, cash equivalents and marketable securities	$3,168,242	$2,088,666	$1,434,557	$1,042,462	$1,387,106
Deferred tax assets (3)	1,499,672	—	—	—	—
Total assets	6,245,898	3,546,014	2,896,787	2,498,587	2,334,679
Total current liabilities (4)	1,120,292	807,260	792,537	506,167	368,254
Long-term debt obligations, excluding current portion	—	—	—	223,863	280,569
Construction financing lease obligation, excluding current portion (5)	561,892	563,406	486,359	472,611	473,073
Other long-term obligations	128,511	133,042	279,700	202,318	116,600

(1) In 2017, we recorded $230.0 million of collaborative and royalty revenues related to an upfront payment made to us pursuant to our collaboration agreement with Merck KGaA, Darmstadt, Germany. See Note B, "Collaborative Arrangements and Acquisitions."

(2) Total costs and expenses included (i) in 2018 and 2017, intangible asset impairment charges of $29.0 million and $255.3 million, respectively, (ii) $111.9 million collaborative expenses in 2018 primarily related to strategic license agreements; $168.7 million collaborative expenses in 2017 primarily related to an asset acquisition and (iii) in 2014, $50.9 million of restructuring charges primarily related to the relocation of our corporate headquarters. See Note J, "Intangible Assets and Goodwill," and Note B, "Collaborative Arrangements and Acquisitions."

(3) In 2018, we released the valuation allowance on the majority of our net operating losses and other deferred tax assets resulting in a benefit from income taxes of $1.56 billion in the fourth quarter of 2018 and we recorded a $1.50 billion deferred tax asset on our consolidated balance sheet as of December 31, 2018. In 2018 and 2017, we recorded benefits from income taxes related to the impairment of intangible assets. See Note J, "Intangible Assets and Goodwill."

(4) As of December 31, 2018 and 2017, we had $354.4 million and $232.4 million, respectively, recorded as current liabilities related to cash received by us for sales of ORKAMBI in France for which the price has not been established. See Note A, "Nature of Business and Accounting Policies."

(5) We have entered into several leases in which we are deemed to be the owner for accounting purposes. See Note L, "Long-term Obligations."

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

OVERVIEW

We invest in scientific innovation to create transformative medicines for people with serious diseases. Our business is focused on developing and commercializing therapies for the treatment of cystic fibrosis, or CF, and advancing our research and development programs in other serious diseases. Our marketed products are SYMDEKO/SYMKEVI (tezacaftor in combination with ivacaftor), ORKAMBI (lumacaftor in combination with ivacaftor) and KALYDECO (ivacaftor), which are collectively approved to treat approximately half of the 75,000 CF patients in North America, Europe and Australia. Our triple combination regimens, if approved, would significantly increase the number of CF patients eligible for our products and could provide an improved treatment option for a majority of the patients currently eligible for our products. In November 2018, we reported positive data, including interim data, from the Phase 3 clinical trials evaluating the triple combination of VX-659, tezacaftor and ivacaftor in patients with a copy of the F508del mutation in their CFTR gene and a second mutation that results in minimal CFTR function, whom we refer to as F508del/Min patients; and who have two copies of the F508del mutation, whom we refer to as F508del homozygous patients. In the first quarter of 2019, we expect to report data from the Phase 3 clinical trials evaluating the triple combination of VX-445, tezacaftor and ivacaftor. We expect that this data in conjunction with the VX-659 data that was reported in November 2018 will enable us to choose the better of the two regimens to submit for regulatory approval. We expect to submit a New Drug Application, or NDA, to the United States Food and Drug Administration, or FDA, for a triple combination regimen no later than mid-2019. We also are developing drug candidates for the treatment of pain, beta-thalassemia, sickle cell disease and alpha-1 antitrypsin deficiency.

2018 Financial Highlights

Revenues:

In 2018, our CF net product revenues continued to increase due to the approval of our third CF medicine, SYMDEKO/SYMKEVI, and increasing KAYLDECO net product revenues. In 2019, we expect our CF net product revenues to continue to increase due to full-year revenues from SYMDEKO/SYMKEVI and further CF net product revenue growth will be dependent on if, and when, we are able to able to obtain approval to market a triple combination regimen for patients with CF.