VERTEX PHARMACEUTICALS INC / MA
Form 10-K
February 15, 2018

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, 2017

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 and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted 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 and post 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

(Do not check if a smaller reporting company)

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. 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 30, 2017 (the last trading day of the registrant's second fiscal quarter of 2017) was $31.8 billion. As of January 31, 2018, the registrant had 253,891,984 shares of common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the definitive Proxy Statement for the 2018 Annual Meeting of Shareholders to be held on May 17, 2018 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.

PART I

ITEM 1. BUSINESS

OVERVIEW

We invest in scientific innovation to create transformative medicines for 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. Our marketed products are ORKAMBI (lumacaftor in combination with ivacaftor), KALYDECO (ivacaftor) and SYMDEKO (tezacaftor in combination with ivacaftor).

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.

Current Medicines

ORKAMBI, KALYDECO and SYMDEKO are collectively approved to treat approximately 45% of the 75,000 CF patients in North America, Europe and Australia. ORKAMBI is approved as a treatment for approximately 28,000 patients who have two copies of the F508del mutation, who we refer to as F508del homozygous patients, in their cystic fibrosis transmembrane conductance regulator, or CFTR, gene. KALYDECO is approved for the treatment of approximately 6,000 CF patients who have the G551D mutation or other specified mutations in their CFTR gene. SYMDEKO was approved by the United States Food and Drug Administration, or FDA, in February 2018 for the treatment of patients with CF twelve years of age and older who are F508del homozygous or who have at least one mutation that is responsive to tezacaftor/ivacaftor, and provides an additional treatment option to CF patients who were already eligible for either ORKAMBI or KALYDECO. We are currently seeking approval from the European Medicines Agency, or EMA, for tezacaftor in combination with ivacaftor.

Next-generation CFTR Corrector Triple Combination Regimens

In the first quarter of 2018, we selected two next-generation corrector compounds, VX-659 and VX-445, to advance into Phase 3 clinical development as part of separate triple combination regimens. Each of VX-659 and VX-445 have the potential to be combined with both (i) tezacaftor and ivacaftor and (ii) tezacaftor and VX-561, a deuterated version of ivacaftor. We expect to initiate the Phase 3 development program for VX-659 in combination with tezacaftor and ivacaftor in the first half of 2018. In mid-2018, we expect to initiate the Phase 3 development of a once-daily combination of VX-445, tezacaftor and VX-561. Our decision to advance VX-659 and VX-445 was based on available clinical and nonclinical data, including data from an ongoing Phase 2 clinical program, and regulatory discussions are ongoing to finalize the design of the Phase 3 development programs for VX-659 and VX-445.

We believe the triple combination regimens we are evaluating could potentially provide benefits to all CF patients who have at least one F508del mutation in their CFTR gene (approximately 90% of all CF patients). This would include (i) the first treatment option that treats the underlying cause of CF for patients who have one copy of the F508del mutation in their CFTR gene and a second mutation in their CFTR gene that results in minimal CFTR function, who we refer to as F508del/Min patients, and (ii) an additional treatment option for patients with CF who are eligible for ORKAMBI, KALYDECO and/or SYMDEKO.

Research and Development Programs

We have a number of ongoing research and development programs in other diseases that we are conducting independently or in collaboration with third parties. We are developing VX-150 and VX-128 as treatments for pain, co-developing CTX001, an investigational gene editing treatment, for the treatment of beta-thalassemia and sickle cell disease, with CRISPR Therapeutics AG, or CRISPR, and developing VX-210 as a treatment for acute spinal cord injury. We plan to continue investing in our research programs and fostering scientific innovation in order to identify and develop transformative medicines. In addition to continuing our research in cystic fibrosis, pain and hemoglobinopathies, our current research programs include programs targeting adrenoleukodystrophy, alpha-1 antritrypsin deficiency and polycystic kidney disease. 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.

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CYSTIC FIBROSIS

Background

CF is a rare, 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. There are more than 2,000 known mutations in the CFTR gene, some of which result in CF. 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 CRTR 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. 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 CF development programs, we refer to our compounds by their scientific (or generic) name.

KALYDECO (ivacaftor)

KALYDECO (ivacaftor) is an orally-administered CFTR potentiator that is approved in the United States, the European Union, Australia and Canada for the treatment of certain patients with CF who have specific mutations in their CFTR gene, including the G551D mutation.

In the fourth quarter of 2017, we obtained results from an open-label Phase 3 clinical trial of KALYDECO in patients with CF one to two years of age with one of 10 mutations in the CFTR gene. The clinical trial met its primary endpoint of safety, showing that KALYDECO was generally well tolerated, and safety data were consistent with those seen in previous Phase 3 clinical trials of ivacaftor in children ages two to five years of age and six to eleven years of age. The clinical trial also showed substantial improvements in sweat chloride, a secondary endpoint, as well as in multiple exploratory endpoints evaluating pancreatic function. Based on these results, we expect to submit regulatory approval applications to the FDA and the EMA for ivacaftor for children ages one to two years in the first quarter of 2018. The Phase 3 clinical trial is ongoing in infants younger than one year old.

ORKAMBI (lumacaftor in combination with ivacaftor)

ORKAMBI is an orally-administered combination therapy comprised of lumacaftor, a CFTR corrector, and ivacaftor that is approved in the United States and European Union for the treatment of specified patients with CF who are homozygous for the F508del mutation in their CFTR gene. ORKAMBI was originally approved in 2015 for the treatment of F508del homozygous patients twelve years of age and older, and we obtained approval for F508del homozygous patients six to eleven years of age in the United States and European Union in September 2016 and January 2018, respectively.

In the fourth quarter of 2017, we obtained results from a 2-part open-label Phase 3 clinical trial of ORKAMBI in 60 patients with CF two to five years of age who have two copies of the F508del mutation in their CFTR gene. The clinical trial met its primary endpoint of safety, showing that ORKAMBI was generally well tolerated and that there were no new safety concerns compared to prior clinical trials of ORKAMBI in patients six through eleven years of age. Secondary endpoints showed decreases in the sweat chloride and improvements in nutritional status as measured by change in weight (weight-for-age z score) and body mass index (BMI-for-age z score). Based on these results, we submitted a New Drug Application, or NDA, to the FDA and expect to submit a Marketing Authorization Application, or MAA, line extension to the EMA in the first quarter of 2018.

SYMDEKO (tezacaftor in combination with ivacaftor)

SYMDEKO is an orally-administered combination therapy comprised of tezacaftor, a CFTR corrector, and ivacaftor that was approved by the FDA in February 2018 for the treatment of patients with CF twelve years of age and older who are F508del homozygous or who have at least one mutation that is responsive to tezacaftor/ivacaftor. The approval was based, in

part, on the results from two Phase 3 clinical trials of tezacaftor in combination with ivacaftor. The clinical trials demonstrated that the tezacaftor/ivacaftor combination provided statistically significant improvements in lung function (percent predicted forced expiratory volume in one second, or ppFEV1) in patients with CF 12 years of age and older who have certain mutations in their CFTR gene. The 24-week EVOLVE clinical trial evaluated tezacaftor in combination with ivacaftor in F508del homozygous patients. This clinical trial met its primary endpoint with a mean absolute improvement in ppFEV1 through 24 weeks of 4.0 percentage points from baseline compared to placebo ($p < 0.0001$). The second clinical trial, EXPAND, was an 8-week crossover clinical trial that evaluated the combination treatment in patients with CF who have one mutation that results in residual CFTR function and one F508del mutation. This clinical trial met the primary endpoints of absolute change in ppFEV1 from baseline to the average of the Week 4 and Week 8 measurements, with the tezacaftor/ivacaftor combination treatment demonstrating a mean absolute improvement of 6.8 percentage points compared to placebo ($p < 0.0001$) and the ivacaftor monotherapy group demonstrating a mean absolute improvement of 4.7 percentage points compared to placebo ($p < 0.0001$). Across both clinical trials, the tezacaftor/ivacaftor combination treatment was generally well tolerated.

We submitted an MAA to the EMA for tezacaftor in combination with ivacaftor. The EMA has validated the MAA and we expect the EMA to complete its review in the second half of 2018.

Next-generation CFTR Corrector Compounds

We are investing significant resources in the development of triple combination regimens that include a next-generation CFTR corrector compound. Over the last two years we have been evaluating four next-generation corrector compounds and have obtained positive clinical data from Phase 1 and Phase 2 clinical trials evaluating triple combination regimens including each of these next-generation corrector compounds. In the first quarter of 2018, we selected two next-generation corrector compounds, VX-659 and VX-445, to advance into Phase 3 clinical development as part of separate triple combination regimens. This decision was based on clinical and nonclinical data, including data from an ongoing Phase 2 clinical program. Regulatory discussions are ongoing to finalize the design of the Phase 3 development programs for VX-659 and VX-445, and we expect additional data from these Phase 2 clinical trials in the first half of 2018. We expect to initiate the Phase 3 development program for VX-659 in combination with tezacaftor and ivacaftor in the first half of 2018. In mid-2018, we expect to initiate the Phase 3 development of VX-445 in combination with tezacaftor and VX-561, which is a deuterated version of ivacaftor, as a once-daily regimen. The initiation of this Phase 3 clinical development program for VX-445 in combination with tezacaftor and VX-561 is subject to the receipt of additional data in the first half of 2018 on the combination of VX-445, tezacaftor and VX-561, including data from the ongoing Phase 2 clinical trial, and completion of long-term non-clinical toxicology studies of VX-445.

We believe the triple combination regimens we are evaluating could potentially provide benefits to all CF patients who have at least one F508del mutation in their CFTR gene (approximately 90% of all CF patients). This would include (i) the first treatment option that treats the underlying cause of CF for F508del/Min patients, and (ii) an additional treatment option for patients with CF who are eligible for ORKAMBI, KALYDECO and/or SYMDEKO.

Next-Generation Clinical Data

VX-659

We are evaluating VX-659 (80mg, 240mg and 400mg QD) in a randomized, double-blind Phase 2 clinical trial in combination with tezacaftor and ivacaftor in two different groups of patients 18 years of age and older who have CF: F508del/Min patients (Part 1), and F508del homozygous patients (Part 2). Minimal function mutations are those that result in little-to-no functioning CFTR protein and are not responsive to ivacaftor, tezacaftor or the combination of tezacaftor and ivacaftor. In Part 3 of the clinical trial we are evaluating VX-659 in combination with tezacaftor and VX-561 in F508del/Min patients as a potential once-daily triple combination regimen. The primary objectives for the clinical trial are safety, tolerability and efficacy as assessed by mean absolute change in ppFEV1 from baseline. Secondary endpoints include change in sweat chloride and Cystic Fibrosis Questionnaire-Revised, or CFQ-R. We have reported data from Part 1 of the clinical trial. Parts 2 and 3 of the clinical trial are ongoing with data expected in the first half of 2018.

Safety Data

In Part 1 of the clinical trial, the triple combination regimen was generally well tolerated. The majority of adverse events were mild or moderate. Serious adverse events were reported in seven patients: three patients in the placebo group (2 with infective pulmonary exacerbations and 1 with decreased pulmonary function test) and four in the triple combination groups (3 with infective pulmonary exacerbations and 1 with influenza). None of these serious adverse events was considered related to treatment and none resulted in treatment discontinuation. The most common adverse events (>10%), regardless of treatment group, were cough, headache, oropharyngeal (throat) pain and sputum increased. There were no discontinuations due to adverse

events. One patient interrupted treatment due to an adverse event in the triple combination treatment groups (rash). The rash resolved following interruption of treatment, and the patient subsequently restarted and completed triple combination treatment without any further incidence.

Efficacy Data

Part 1 of the clinical trial evaluated the triple combination for four weeks in 63 F508del/Min patients (10 in the placebo arm, 11 in the VX-659 80mg arm, 20 in the VX-659 240mg arm and 22 in the VX-659 400mg arm). A summary of the within-group lung function and sweat chloride data is provided below:

VX-659 in F508del/Min Patients

Mean Absolute Within-Group Change From Baseline Through Day 29*	Mean Absolute Within-Group Change in ppFEV$_1$ (percentage points)	Mean Absolute Within-Group Change in Sweat Chloride (mmol/L)
Triple placebo	+0.3 (p=0.9053)	+2.9 (p=0.5338)
VX-659 (80mg QD) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+10.2 (p=0.0004)	-45.8 (p<0.0001)
VX-659 (240mg QD) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+11.6 (p<0.0001)	-43.7 (p<0.0001)
VX-659 (400mg QD) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+13.3 (p<0.0001)	-51.4 (p<0.0001)

* all p-values are within group p-values based on mixed effect models; values expressed as ‘Through Day 29' are the average of Day 15 and Day 29 measures

A secondary endpoint in the clinical trial measured mean absolute change in the respiratory domain of CFQ-R, a validated patient-reported outcome measure, at Day 29. CFQ-R results reported are based on a mixed effect model not adjusted for baseline CFQ-R. The mean absolute improvements for patients who received the triple combination were 24.6 points (VX-659 80mg arm), 19.8 points (VX-659 240mg arm) and 21.8 points (VX-659 400mg arm). The improvement for those who received placebo was 4.7 points.

VX-445

We are evaluating VX-445 in an ongoing Phase 2 randomized, double-blind clinical trial. In this clinical trial, we are evaluating the safety and tolerability of single and multiple ascending doses of VX-445 alone and in triple combination with tezacaftor and ivacaftor in healthy volunteers (Parts A, B and C). We also are evaluating the safety, tolerability and efficacy of VX-445 (50mg, 100mg and 200mg QD) in triple combination with tezacaftor and ivacaftor for four weeks in patients with CF 18 years of age and older who are F508del/Min patients (Part D) and F508del homozygous patients (Part E). In Part F of the clinical trial, we are evaluating VX-445 in combination with tezacaftor and VX-561 as a potential once-daily triple combination regimen in F508del/Min patients. The primary objectives of the parts of the clinical trial in CF patients are safety, tolerability and efficacy as assessed by mean absolute change in ppFEV1 from baseline. Secondary endpoints include change in sweat chloride and CFQ-R. We have reported data from Part D of the clinical trial. Parts E and F of the clinical trial are ongoing with data expected in the first half of 2018.

Safety Data

In Part D of the clinical trial, the triple combination regimen was generally well tolerated. The majority of adverse events were mild or moderate. Serious adverse events were reported in five patients: two patients in the placebo group (1 with hemoptysis and 1 with infective pulmonary exacerbation) and three patients in the triple combination groups (1 patient with infective pulmonary exacerbation, jugular vein thrombosis related to a central line and distal intestinal obstruction syndrome; 1 patient with infective pulmonary exacerbation and influenza; and 1 patient with infective pulmonary exacerbation). None of these serious adverse events was considered related to treatment and none resulted in treatment discontinuation. The most common adverse events (>10%), regardless of treatment group, were cough, sputum increased, infective pulmonary exacerbation, hemoptysis, headache, nasal congestion, nausea, oropharyngeal pain and pyrexia. Two patients discontinued treatment due to adverse events in the triple combination treatment groups (1 patient with rash and 1 patient with increased bilirubin without associated elevations in transaminases) and none in the placebo group. Following treatment discontinuation, the rash resolved and the increased bilirubin returned to baseline. Two patients interrupted treatment due to adverse events in the triple combination groups (1 with

constipation and 1 with increased bilirubin without associated elevations in transaminases); both events resolved when treatment was interrupted and both patients subsequently restarted and completed triple combination treatment without further incident.

Efficacy Data

Part D of the clinical trial evaluated the triple combination for four weeks in 65 patients who have one F508del mutation and one minimal function mutation (12 in the combined placebo arm, 10 in the VX-445 50mg arm, 22 in the VX-445 100mg arm and 21 in the VX-445 200mg arm). A summary of the within-group lung function and sweat chloride data is provided below:

VX-445 in F508del/Min Patients

Mean Absolute Within-Group Change From Baseline Through Day 29*	Mean Absolute Within-Group Change in $ppFEV_1$ (percentage points)	Mean Absolute Within-Group Change in Sweat Chloride (mmol/L)
Triple placebo	0.0 (p=0.9943)	-2.2 (p=0.5804)
VX-445 (50mg QD) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+11.1 (p<0.0001)	-38.2 (p<0.0001)
VX-445 (100mg QD) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+7.8 (p<0.0001)	-33.2 (p<0.0001)
VX-445 (200mg QD) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+13.8 (p<0.0001)	-39.1 (p<0.0001)

* all p-values are within group p-values based on mixed effect models; values expressed as ‘Through Day 29' are the average of Day 15 and Day 29 measures

A secondary endpoint in the clinical trial measured mean absolute change in the respiratory domain of CFQ-R at Day 29. CFQ-R results reported are based on a mixed effect model not adjusted for baseline CFQ-R. The mean absolute improvements for patients who received the triple combination were 20.8 points (VX-445 50mg arm), 15.4 points (VX-445 100mg arm) and 25.7 points (VX-445 200mg arm). The improvement for those who received placebo was 4.2 points.

DEVELOPMENT PROGRAMS

Pain

We are developing VX-150 and VX-128, inhibitors of the sodium channel 1.8 (Nav 1.8), as potential treatments for pain. We have obtained positive results from two 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 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.

A third Phase 2 clinical trial evaluating VX-150 for the treatment of neuropathic pain caused by small fiber neuropathy is ongoing, and we are planning to initiate a Phase 1 clinical trial of an intravenous formulation of VX-150.

A Phase 1 clinical trial of VX-128, in healthy volunteers is ongoing to evaluate single and multiple ascending doses of VX-128 to support the planned initiation of a Phase 2 clinical trial of VX-128 in acute pain.

Hemoglobinopathies

In conjunction with CRISPR, we are co-developing a treatment aimed at the underlying genetic causes of specified hemoglobinopathies using CRISPR-Cas9 gene editing technology. In the fourth quarter of 2017, CRISPR submitted a clinical trial application for CTX001, an investigational gene editing treatment, in beta-thalassemia, a blood disorder that reduces the production of hemoglobin. The Phase 1/2 trial is designed to assess the safety and efficacy of CTX001 in adult transfusion-dependent beta-thalassemia patients and is expected to begin in Europe in 2018. In 2018, we expect an investigation new drug, or IND, application to be submitted to the FDA for CTX001 as a potential treatment for sickle cell disease.

Influenza

Janssen Pharmaceuticals, Inc., or Janssen, is developing pimodivir (JNJ-63623872), previously referred to as VX-787, as a potential treatment for the influenza A virus. We exclusively licensed pimodivir to Janssen in 2014. During the fourth quarter of 2017, Janssen initiated a Phase 3 clinical trial of pimodivir in combination standard of care treatment in patients who are hospitalized or are outpatients at a higher risk of influenza-related complications.

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RESEARCH PROGRAMS

We invest in research and development in order to discover and develop medicines for people with serious diseases. Our research organization seeks to identify new medicines by combining transformative insights into the causal human biology of serious diseases with innovative approaches to therapeutics. 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 for the treatment of cystic fibrosis and INCIVEK (telaprevir) for the treatment of hepatitis C infection. 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. 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. For example, in the fourth quarter of 2017, a clinical trial application was submitted for CTX001, a drug candidate that we are co-developing with CRISPR that utilizes the CRISPR-Cas9 gene editing technology.

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

- focusing on validated targets that have been shown in patients to have a causal relationship with respect to serious diseases;
- 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; and
- identifying efficient clinical and regulatory paths to bring new medicines to patients.

In addition to continuing our research to identify additional drug candidates for the treatment of cystic fibrosis, pain and hemoglobinopathies, we are focusing our early research efforts on identifying drug candidates for the treatment of serious diseases such as adrenoleukodystrophy, alpha-1 antritrypsin deficiency and polycystic kidney disease.

To augment our internal research 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.

COMMERCIAL ORGANIZATION

Our commercial organization focuses on supporting sales of ORKAMBI, KALYDECO and SYMDEKO 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 will be sufficient to support future needs, including support for SYMDEKO which was recently approved by the FDA. 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 a small sales force that promotes KALYDECO and ORKAMBI in jurisdictions where these products are approved.

We market our products through personal interactions with individual physicians, advertising, sending direct mail, public relations activities and other activities. 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.

COLLABORATIONS

We have entered into collaborations with pharmaceutical and other companies and organizations that provide us financial and other resources, including capabilities in research, development, manufacturing and sales and marketing, and licenses to

intellectual property. These collaborations have provided us with drug candidates and/or important financial and non-financial resources that have contributed to our products and a number of the drug candidates in our current development pipeline. We may seek to license or acquire drugs, drug candidates and other technologies that have the potential to add to our pipeline or to provide us with new commercial opportunities. In particular, we are focusing on drug candidates for the treatment of patients with CF and other third-party drug candidates that could be developed for specialty markets. Furthermore, we may seek collaborators to support, develop and/or commercialize some of our current drug candidates and/or additional drug candidates that may emerge from our research activities.

Cystic Fibrosis Foundation Therapeutics Incorporated

We began working with the Cystic Fibrosis Foundation Therapeutics Incorporated, or CFFT, in 1998. We entered into a collaboration agreement with CFFT in 2004 and have amended it several times 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 (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, sales are allocated equally to each of the active pharmaceutical ingredients in the combination product.

For ivacaftor, lumacaftor and tezacaftor, we will have royalty obligations to CFFT until the expiration of patents covering each compound. We have patents in the United States and European Union covering the composition-of-matter of ivacaftor that expire in 2027 and 2025, respectively, subject to potential patent life extensions. We have patents in the United States and European Union covering the composition-of-matter of lumacaftor that expire in 2030 and 2026, respectively, subject to potential patent life extensions. We have patents in the United States and European Union covering the composition-of-matter of tezacaftor that expire in 2027 and 2028, respectively, subject to potential patent life extensions.

CRISPR Therapeutics AG

In 2015, we entered into a strategic collaboration, option and license 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. Pursuant to this agreement, we have the exclusive right to license up to six CRISPR-Cas9-based targets and paid CRISPR an upfront payment of $75.0 million.

We fund all of the discovery activities conducted pursuant to the CRISPR agreement. For potential hemoglobinopathy treatments, including treatments for sickle cell disease and beta-thalassemia, we share equally with CRISPR all research and development costs and worldwide revenues. For other targets that we elect to license, we would lead all development and global commercialization activities. For each target that we elect to license, other than hemoglobinopathy targets, CRISPR has the potential to receive up to $420.0 million in development, regulatory and commercial milestones and royalties on net sales.

We may terminate the agreement upon 90 days' notice to CRISPR prior to any product receiving marketing approval or upon 270 days' notice after a product has received marketing approval. The agreement also may be terminated by either party for a material breach by the other, subject to notice and cure provisions. Unless earlier terminated, the agreement will continue in effect until the expiration of our payment obligations under the agreement.

In the fourth quarter of 2017, pursuant to the terms of the agreement, we entered a co-development and co-commercialization agreement with CRISPR, under which we and CRISPR will co-develop and co-commercialize CTX001 for the treatment of hemoglobinopathies.

Other Collaborations

Moderna Therapeutics, Inc.

In July 2016, we entered into a strategic collaboration and licensing agreement with Moderna Therapeutics, Inc., or Moderna, pursuant to which the parties are seeking to identify and develop messenger ribonucleic acid, or mRNA, therapeutics for the treatment of CF. In connection with this agreement, we made an upfront payment to Moderna of $20.0 million. Moderna has the potential to receive future development and regulatory milestones of up to $275.0 million, including $220.0 million in approval and reimbursement milestones, as well as tiered royalty payments on net

sales. Under the terms of the Moderna agreement, Moderna is leading discovery efforts and we are leading all preclinical, development

and commercialization activities associated with the advancement of mRNA therapeutics that result from this collaboration and we will fund all expenses related to the collaboration.

We may terminate the agreement by providing advance notice to Moderna, with the required length of notice dependent upon whether any product developed under the agreement has received marketing approval. The agreement also may be terminated by either party for a material breach by the other, subject to notice and cure provisions. Unless earlier terminated, the agreement will continue in effect until the expiration of our payment obligations under the agreement.

BioAxone Biosciences, Inc.

In 2014, we entered into a license and collaboration agreement with BioAxone. Pursuant to this agreement, we are collaborating with BioAxone on the research, development and commercialization of VX-210 (formerly referred to as Cethrin), a Rho inhibitor controlled by BioAxone, for the treatment of patients who have spinal cord injuries.

We paid BioAxone an initial payment of $10.0 million and BioAxone has the potential to receive up to $90.0 million in milestones and license fees, including development and regulatory milestone payments and a license continuation fee. In addition, BioAxone would receive tiered royalties and commercial milestones based on future net product sales, if any. We hold an option to purchase BioAxone at a predetermined price. The option expires on the earliest of (a) the day the FDA accepts the Biologics License Application submission for VX-210, (b) the day we elect to continue the license instead of exercising the option to purchase BioAxone and (c) March 15, 2018, subject to our option to extend this date by one year. We may terminate our agreement with BioAxone upon 90 days' notice or immediately if we determine that a licensed product is unsafe for administration to humans. The agreement also may be terminated by either party for a material breach by the other or by BioAxone for our inactivity with respect to VX-210, in each case subject to notice and cure provisions. Unless earlier terminated, the agreement will continue until the expiration of our royalty obligations.

Parion Sciences, Inc.

In 2015, we entered into a strategic collaboration and license agreement with Parion Sciences, Inc., or Parion, pursuant to which we are collaborating with Parion to develop ENaC inhibitors, including VX-371 and VX-551, for the potential treatment of CF and other pulmonary diseases.

Parion received an $80.0 million up-front payment and in 2016, Parion earned a milestone payment of $5.0 million based upon the achievement of a specified milestone under the agreement. Parion has the potential to receive up to an additional (i) $485.0 million in development and regulatory milestone payments for development of ENaC inhibitors in CF, including $360.0 million related to global filing and approval milestones, (ii) $370.0 million in development and regulatory milestones for VX-371 and VX-551 in non-CF pulmonary indications and (iii) $230.0 million in development and regulatory milestones if we elect to develop an additional ENaC inhibitor from Parion's research program. Parion will receive tiered royalties on potential sales of licensed products that range from the low double digits to mid-teens as a percentage of net sales.

We may terminate the agreement upon 90 days' notice to Parion prior to any licensed product receiving marketing approval or upon 180 days' notice after a licensed product has received marketing approval. Parion may terminate the agreement upon 30 days' notice if Vertex experiences a change of control prior to the initiation of the first Phase 3 clinical trial for a licensed product, subject to our right to receive specified royalties on any subsequent commercialization of licensed products. The agreement also may be terminated by either party for a material breach by the other, subject to notice and cure provisions. Unless earlier terminated, the agreement will continue in effect until the expiration of our royalty obligations.

Outlicense Arrangements

We have entered into various agreements pursuant to which we have outlicensed rights to certain drug candidates to third-party collaborators. Pursuant to these outlicense arrangements, our collaborators become 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 product research and development objectives and/or pay royalties on future sales, if any, of commercial products resulting from the collaboration.

Merck KGaA

In the first quarter of 2017, we entered into a Strategic Collaboration and License Agreement with Merck KGaA, Darmstadt, Germany, or Merck KGaA. Pursuant to the agreement, we granted Merck KGaA an exclusive worldwide license to research, develop and commercialize four oncology research and development programs. Under the agreement, we granted Merck KGaA exclusive, worldwide rights to our two clinical-stage programs targeting DNA damage repair: our

ataxia telangiectasia and Rad3-related protein inhibitor, or ATR program, including VX-970 and VX-803, and our DNA-dependent protein kinase inhibitor, or DNA-PK program, including VX-984. In addition, we granted Merck KGaA exclusive, worldwide rights to two pre-clinical programs.

Under the agreement, we earned an up-front payment of $230.0 million. In addition, we will receive tiered royalties on potential sales of licensed products, calculated as a percentage of net sales, that range from (i) mid-single digits to mid-twenties for clinical-stage programs and (ii) mid-single digits to high single digits for the pre-clinical research programs. Merck KGaA will assume full responsibility for development and commercialization costs for all programs. Merck KGaA may terminate the agreement or any individual program by providing 90 days' notice, or, in the case of termination of a program with a product that has received marketing approval, 180 days' notice. The agreement may also be terminated by either party for a material breach by the other party, subject to notice and cure provisions. Unless earlier terminated, the agreement will continue in effect until the date on which the royalty term and all payment obligations with respect to all products in all countries have expired.

Janssen Pharmaceuticals, Inc.

In 2014, we entered into an agreement with Janssen Inc. Pursuant to this agreement, Janssen Inc. has an exclusive worldwide license to develop and commercialize certain drug candidates for the treatment of influenza, including JNJ-63623872 (formerly VX-787). We received non-refundable payments of $35.0 million from Janssen Inc. in 2014 and have the potential to receive development, regulatory and commercial milestone payments as well as royalties on future product sales, if any. Janssen Inc. is responsible for costs related to the development and commercialization of the compounds. Janssen Inc. may terminate the agreement, subject to certain exceptions, upon six months' notice. In the fourth quarter of 2017, we earned a $25.0 million milestone payment from Janssen Inc. related to the initiation of a Phase 3 clinical trial of JNJ-63623872.

INTELLECTUAL PROPERTY

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. We have patents and pending patent applications that relate to potential drug targets, compounds we are developing to modulate those targets, methods of making or using those compounds and proprietary elements of our drug discovery platform.

Much of our technology and many of our processes depend upon the knowledge, experience and skills of key scientific and technical personnel. To protect our rights to our proprietary know-how and technology, we require all employees, as well as our consultants and advisors when feasible, to enter into confidentiality agreements that require disclosure and assignment to us of ideas, developments, discoveries and inventions made by these employees, consultants and advisors in the course of their service to us.

While we have numerous issued patents and pending patent applications in our patent portfolio, we believe that the patents and patent applications in the United States and the European Union that are the most important to our business are those that claim the composition-of-matter of our drugs and drug candidates that have progressed at least into Phase 3 clinical trials. The following table sets forth the status of such primary patents and patent applications in the United States and the European Union covering the composition-of-matter of these drugs and drug candidates:

Drug/Drug Candidate	Status of United States Patent (Anticipated Expiration, Subject to Potential Extensions)	Status of European Union Patent (Anticipated Expiration, Subject to Potential Extensions)
Ivacaftor	Granted (2027)	Granted (2025)
Lumacaftor	Granted (2030)	Granted (2026)
Tezacaftor	Granted (2027)	Granted (2028)

We hold issued patents and pending patent applications in the United States, and in foreign countries we deem appropriate, claiming intellectual property developed as part of our research and development programs. In addition to the composition-of-matter patents and patent applications listed above, we hold or have exclusive licenses to the following intellectual property:

- U.S. and foreign patents and patent applications covering CF potentiators, correctors and ENaC inhibitors, including ivacaftor, lumacaftor, tezacaftor, VX-561, VX-659, VX-445 and VX-371 and many other related compounds, and the use of those potentiators, correctors and ENaC inhibitors to treat CF.

- U.S. and foreign patents and patent applications covering VX-150 and VX-128 and the use of VX-150 and VX-128 to treat pain indications.
- U.S. and foreign patents and patent applications covering VX-210 and the use of VX-210 to treat neurology indications.
- U.S. and foreign patents and patent applications covering the manufacture, pharmaceutical compositions, related solid forms, formulations, dosing regimens and methods of use of most of the above compounds, including ivacaftor, lumacaftor and tezacaftor.

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

We have a U.S. patent that covers the composition-of-matter of ivacaftor that we expect will provide intellectual property protection in the United States through its expiration date in 2027. We have a European patent that covers the composition-of-matter of ivacaftor that we expect will provide intellectual property protection in the European Union through its expiration date in 2025, subject to potential extension.

We have patents in the United States and European Union that cover the composition of matter of lumacaftor that we expect will provide intellectual property protection in these jurisdictions through their expiration dates in 2030 and 2026, respectively, subject to potential extension.

We have patents in the United States and European Union that cover the composition of matter of tezacaftor that we expect will provide intellectual property protection in these jurisdictions through their expiration dates in 2027 and 2028, respectively, subject to potential extension.

MANUFACTURING

Manufacturing Approach and Philosophy

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. Wherever possible, we seek to establish multiple suppliers for each raw material and step in the manufacturing process. However, our supply chain includes a single-source manufacturer for (i) one step in the ivacaftor manufacturing process, (ii) the manufacture of the tablets of ORKAMBI that is used for patients with CF six to eleven years of age and (iii) a pre-formulation step and the manufacture of the tablets for our commercial supply of SYMDEKO.

We expect that we will continue for the foreseeable future to rely on third parties to meet most of 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.

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

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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.

Manufacture of KALYDECO (ivacaftor)

We obtain ivacaftor to meet our commercial and clinical supply needs through a third-party manufacturing network. A disruption in the commercial supply of KALYDECO would have a significant effect on patients, our business and our product revenues.

Manufacture of ORKAMBI (lumacaftor/ivacaftor)

We obtain the bulk materials needed to produce both our commercial and clinical supply of ORKAMBI through a third-party manufacturing network. We have developed several tablet manufacturing processes utilizing various degrees of continuous manufacturing technology as well as a batch manufacturing processes to produce commercial quantities of ORKAMBI. This includes multiple third-party manufacturers that are producing commercial quantities of ORKAMBI using combinations of batch and continuous manufacturing processes, as well as a fully-continuous drug product manufacturing process at our internal facility located in Boston, Massachusetts. 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.

Manufacture of SYMDEKO (tezacaftor/ivacaftor)

We obtain the bulk materials needed to produce both our commercial and clinical supply of SYMDEKO through a third-party manufacturing network. We produce our commercial supply of SYMDEKO using a fully-continuous drug product manufacturing process at our internal facility located in Boston, Massachusetts and are in the process of establishing a second fully-continuous drug product manufacturing location with a third-party.

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. Many of our competitors have substantially greater financial, technical and human resources than we do. We face competition based on the safety and efficacy of our products 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

An increasing number of companies are seeking to identify and develop drug candidates for the treatment of CF, including companies such as Galapagos NV in collaboration with AbbVie, ProQR Therapeutics, Proteostasis Therapeutics, Eloxx Pharmaceuticals and several private companies. Although we are the first company to successfully develop drugs that treat the underlying cause of CF, ORKAMBI, KALYDECO and SYMDEKO are collectively approved to treat only a portion of patients with CF. Our competitors have research and development programs directed at identifying and developing 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 competitors are exploring the development of drug candidates primarily as part of combination regimens. Our success in rapidly developing and commercializing KALYDECO, ORKAMBI and SYMDEKO 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

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with CF, our revenues from ORKAMBI, KALYDECO, SYMDEKO and/or our other CF drug candidates, 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 regulation. federal and state statutes and regulations govern the testing, manufacture, safety, efficacy, 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, FDA regulations and guidance often are revised or reinterpreted by the agency in ways that may significantly affect our business and our products. It is impossible to predict whether legislative changes will be enacted, or FDA 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 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.

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"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, 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;

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- 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.

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.

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 will 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 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 ORKAMBI and KALYDECO and of any other drug candidates we may develop, 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.

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 “sunshine” provisions. The 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 made to physicians and certain other healthcare practitioners or to teaching hospitals. 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, 2017, we had approximately 2,300 employees, as compared to approximately 2,150 employees as of December 31, 2016. Of these employees, approximately 1,870 were based in the United States and approximately 375 were based in Europe. In February 2017, we decided to consolidate our research activities into our Boston, Milton Park and San Diego locations and closed our research site in Canada. Our scientific staff members have diversified experience and expertise in molecular and cell biology, genetics, biochemistry, synthetic organic chemistry, protein X-ray crystallography, protein nuclear magnetic resonance spectroscopy, microbiology, computational chemistry and computational biology, biophysical chemistry, medicinal chemistry, clinical pharmacology and clinical medicine. Our clinical development personnel have extensive expertise in designing and executing clinical trials. Employees in our commercial organization have extensive experience in selling and marketing pharmaceutical products as well as seeking reimbursement from government and third-party payors for pharmaceutical products. Our employees are not covered by a collective bargaining agreement, except for a small number of employees outside the U.S. We consider our relations with our employees to be good.

OTHER MATTERS

Financial Information and Significant Customers

Financial information about (i) our net product revenues and other revenues generated in the principal geographic regions in which we operate and our significant customers is set forth in Note T, “Segment Information,” to our consolidated financial statements included in this Annual Report on Form 10-K, (ii) net income (loss) per share attributable to Vertex common shareholders and our total assets are provided in our consolidated financial statements included in this Annual Report on Form 10-K and (iii) our research and development expenses in each of the last three fiscal years and our deconsolidation of Parion as of September 30, 2017 is provided in Item 7, “Management’s Discussion and Analysis of Financial Condition and Results of Operations.” A discussion of the risks attendant to our international operations is set forth in the “Risk Factors” section of 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.	62	Chairman of the Board, Chief Executive Officer and President
David Altshuler, M.D., Ph.D.	53	Executive Vice President, Global Research and Chief Scientific Officer
Stuart A. Arbuckle	52	Executive Vice President and Chief Commercial Officer
Jeffrey A. Chodakewitz, M.D.	62	Executive Vice President, Global Medicines Development and Medical Affairs, and Chief Medical Officer
Michael Parini, J.D.	43	Executive Vice President and Chief Legal and Administrative Officer
Amit K. Sachdev, J.D.	50	Executive Vice President and Chief Regulatory Officer
Ian F. Smith	52	Executive Vice President and Chief Operating Officer
Thomas Graney	53	Senior Vice President and Chief Financial Officer
Paul M. Silva	51	Senior Vice President and Corporate Controller
Sangeeta M. Bhatia, M.D., Ph.D.	49	Director
Alan Garber, M.D., Ph.D.	62	Director
Terrence C. Kearney	63	Director
Yuchun Lee	52	Director
Margaret G.	58	Director

McGlynn Bruce I. Sachs	58	Director
Elaine S. Ullian	70	Director
William Young	73	Director

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 is a senior advisor to Clarus Ventures. 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, MIT, 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. Chodakewitz is our Executive Vice President, Global Medicines Development and Medical Affairs and Chief Medical Officer. Dr. Chodakewitz joined Vertex as a Senior Vice President in January 2014 and became an Executive Vice President in October 2014. Prior to joining us, Dr. Chodakewitz spent more than 20 years at Merck & Co., Inc., where he held a variety of roles including Vice President of Clinical Research – Infectious Diseases & Vaccines, Vice President of Clinical Pharmacology/Early Stage Development, Senior Vice President of Late Stage Development, and Senior Vice President of Global Scientific Strategy (Infectious Diseases, Respiratory/Immunology). Prior to his tenure at Merck, he served as the Director of the HIV Outpatient Clinic at the Veterans Administration Medical Center in West Haven, Connecticut and held various academic positions at Yale University and New York University Schools of Medicine. Dr. Chodakewitz serves as a member of the Board of Directors of Tetraphase Pharmaceuticals, Inc., a pharmaceutical company. Dr. Chodakewitz holds B.S. in Biochemistry from Yale University, and an M.D. from the Yale 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. Smith is our Executive Vice President and Chief Operating Officer, a role he assumed in September 2017. He was our Executive Vice President, Chief Operating Officer and Chief Financial Officer from January 2017 until September 2017, Executive Vice President and Chief Financial Officer from February 2006 until January 2017, our Senior Vice President and Chief Financial Officer from November 2003 to February 2006, and our Vice President and Chief Financial Officer from October 2001 to November 2003. Prior to joining us, Mr. Smith served as a partner in the Life Science and Technology Practice Group of Ernst & Young LLP, an accounting firm, from 1999 to 2001. Mr. Smith initially joined Ernst & Young's U.K. firm in 1987, and then joined its Boston office in 1995. Mr. Smith has served as a member of the Boards of Directors of Acorda Therapeutics, Inc., a drug development company, since February 2007, and Infinity Pharmaceuticals, Inc., a drug development company, since May 2008. Mr. Smith served on the Board of Directors of Ophthotech Corporation, a biopharmaceutical company, from August 2016 to May 2017. Mr. Smith holds a B.A. in accounting and finance from Manchester Metropolitan University, U.K., is a member of the American Institute of Certified Public Accountants and is a Chartered Accountant of England and Wales.

Mr. Graney is our Senior Vice President and Chief Financial Officer, a position he has held since September 2017. From August 2014 until he joined Vertex, Mr. Graney served as Chief Financial Officer and Senior Vice President of Finance and Corporate Strategy for Ironwood Pharmaceuticals, Inc. From January 2010 to August 2014, Mr. Graney served as Worldwide Vice President of Finance and Chief Financial Officer of Ethicon, Inc., a maker of surgical medical devices and subsidiary of Johnson and Johnson. From 1994 to 2010, Mr. Graney served in various roles of increasing responsibility at Johnson & Johnson, including most recently as Vice President of Finance for J&J Global

Supply Chain. Mr. Graney serves on the board of directors of AC Immune SA, a biopharmaceutical company. Mr. Graney holds a Bachelor of Science degree in accounting from the University of Delaware and an M.B.A. in marketing, finance and international business from the Leonard N. Stern School of Business at New York University.

Mr. Silva is our Senior Vice President and Corporate Controller, a position he has held since April 2011. 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 financing 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, where she currently serves as the John J. and Dorothy Wilson Professor of Health Sciences & Technology/Electrical Engineering & Computer Science. 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, the American Academy for Arts and Sciences, and the Board on Science, Technology, and Economic Policy at the National Academies. 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 has also 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, and AveXis, Inc., a gene therapy company, and served as a member of the Board of Directors at Innoviva, Inc. (formerly known as Theravance, Inc.), a royalty management company, until April 2016. 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 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 July 2011 until September 2015. Ms. McGlynn served as President, Vaccines and Infectious Diseases of Merck & Co., Inc. from 2005 until

2009. Ms. McGlynn joined Merck in 1983 and served in a variety of marketing, sales and managed care roles. 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. and Hologic, Inc. 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 Venture Partner at Clarus Ventures, a life sciences venture capital firm, which he joined 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 from Biogen’s Board of Directors 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 or if we do not meet the expectations of investors or public equity market analysts, our business would be materially harmed and the market price of our common stock would likely decline.

Substantially all of our net product revenues and the vast majority of our total revenues are derived from the sale of CF medicines. ORKAMBI and KALYDECO net product revenues represented approximately 53% and 34% of our total revenues in the year ended December 31, 2017, 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, including SYMDEKO which was approved by the FDA in February 2018. 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 patients who have one copy of the F508del mutation in their CFTR gene and a second mutation in their CFTR gene that results in minimal CFTR function 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.

Additionally, 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, ORKAMBI, KALYDECO and SYMDEKO, as well as one or more of our drug candidates, may be adversely affected.

If one or more of the above risks were to materialize or if we are otherwise unable to increase revenues from sales of our CF medicines, 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 compounds, 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, and recently selected VX-659 and VX-445 to evaluate in Phase 3 clinical development as part of 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. We are planning to initiate Phase 3 clinical development of VX-659 in the first half of 2018 and VX-445 in mid-2018 based on ongoing Phase 2 clinical trials that enrolled a limited number of patients with CF. We expect to receive additional information regarding these combination regimens, including additional data from these ongoing Phase 2 clinical trials of VX-659 and VX-445 and long-term nonclinical toxicology studies of VX-445, in the first half of 2018, which could adversely affect our planned initiation of Phase 3 clinical trials for these regimens.

In order to ultimately obtain approval for a triple combination regimen, we will need to demonstrate that the compounds are safe and effective in a significantly larger number of patients than were involved in the clinical trials conducted to date. Initial results from ongoing clinical trials may differ materially from final results from such clinical trials. The results from preclinical and early clinical studies do not always accurately predict results in later,

large-scale clinical trials. If the data

from our ongoing or planned clinical trials or non-clinical studies of triple combination regimens including our next-generation CFTR compounds 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 that includes a next-generation CFTR corrector compounds 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.

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 experien