VERTEX PHARMACEUTICALS INC / MA
Form 10-K
February 13, 2015

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, 2014

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. o

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer or a smaller reporting company. See definitions of “large accelerated filer,” “accelerated filer” and “smaller reporting 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
(Do not check if a smaller reporting company)

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, 2014 (the last trading day of the registrant’s second fiscal quarter of 2014) was $22.4 billion. As of January 31, 2015, the registrant had 242,088,884 shares of common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the definitive Proxy Statement for the 2015 Annual Meeting of Shareholders to be held on June 4, 2015 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 are in the business of discovering, developing, manufacturing and commercializing small molecule drugs. We use precision medicine approaches to create transformative drugs for patients with serious diseases in specialty markets. Our business is focused on developing and commercializing therapies for the treatment of cystic fibrosis, or CF, and advancing our research and early-stage development programs, while maintaining our financial strength.

Cystic Fibrosis

Our goal is twofold: to develop treatment regimens that will provide benefits to as many patients with CF as possible and to enhance those benefits.

KALYDECO

KALYDECO (ivacaftor) was approved in 2012 in the United States and European Union as a treatment for patients with CF six years of age and older who have the G551D mutation in their cystic fibrosis transmembrane conductance regulator, or CFTR, gene. In 2014, we increased the number of patients who are being treated with KALYDECO in the United States and non-U.S. markets by expanding the label for KALYDECO to include patients with CF six years of age and older who have additional mutations in their CFTR gene. In addition, we have submitted applications to regulatory authorities to further expand the label for KALYDECO to include patients with CF two to five years of age with specific gating mutations in their CFTR gene and to include patients with CF 18 years of age and older in Europe who have the R117H mutation in their CFTR gene.

Lumacaftor in Combination with Ivacaftor

In June 2014, we announced data from two Phase 3 clinical trials, referred to as TRAFFIC and TRANSPORT, of lumacaftor, a CFTR corrector compound, in combination with ivacaftor, a CFTR potentiator compound. In TRAFFIC and TRANSPORT, we evaluated the combination regimen in patients with CF twelve years of age and older who have two copies (homozygous) of the F508del mutation in their CFTR gene, which is the most prevalent form of CF. In November 2014, we submitted a New Drug Application, or NDA, to the United States Food and Drug Administration, or FDA, and a Marketing Authorization Application, or MAA, to the European Medicines Agency, or EMA, for lumacaftor in combination with ivacaftor. The FDA has granted us priority review of the NDA and the target date for the FDA to complete its review of the NDA under the Prescription Drug User Fee Act, or PDUFA, is July 5, 2015. Our request for Accelerated Assessment of the MAA has been granted, and we expect the EMA to complete its review of the MAA in the fourth quarter of 2015.

VX-661 in Combination with Ivacaftor

In 2015, we initiated a Phase 3 development program for VX-661 in combination with ivacaftor in patients with CF twelve years of age and older, including patients who are homozygous for the F508del mutation in their CFTR gene and patients with CF who have one copy of the F508del mutation in their CFTR gene (heterozygous).

CF Research Programs

We also are seeking to identify and develop next-generation CFTR corrector compounds that could be evaluated in future dual- and/or triple-combination treatment regimens with the potential to provide additional benefits to patients with CF. We have multiple next-generation correctors in the lead-optimization stage of research and expect to begin clinical development of a next-generation corrector in 2015.

Research and Early-stage Development Programs

We are engaged in a number of other research and early-stage development programs, including programs in the areas of oncology and neurology. We plan to continue investing in our research programs and fostering scientific innovation in order to identify and develop transformative medicines with a focus on CF and other genetic diseases, oncology and neurology. We believe that pursuing research in diverse areas allows us to balance the risks inherent in drug development and may provide drug candidates that will form our pipeline in future years.

CYSTIC FIBROSIS

Background

CF is a rare, life-threatening 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 from each parent. There are more than 1,900 known mutations in the CFTR gene, some of which result in CF, including two of the most prevalent mutations, the G551D mutation and the F508del mutation.

The G551D mutation results in a defect in the CFTR protein in which the defective CFTR protein reaches the surface of a cell but does not efficiently transport chloride ions across the cell membrane. The F508del mutation results in a defect in the CFTR protein in which the CFTR protein does not reach the surface of cells in sufficient quantities. 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. Patients with CF often experience pulmonary exacerbations and periods of worsening signs or symptoms of the disease, often requiring treatment with antibiotics and/or hospitalization. Ivacaftor, a CFTR potentiator, keeps the CFTR protein channels on the cell surface open more often, to increase the flow of salt and water into and out of the cell. CFTR correctors, such as lumacaftor and VX-661, are believed to help CFTR protein reach the cell surface.

We chose to develop KALYDECO (ivacaftor) and our other CF drug candidates because of their potential to improve the function of defective CFTR proteins in patients with CF, which is the underlying cause of CF. Our research group is continuing to work to identify additional corrector compounds that could be included in future dual- and/or triple-combination treatment regimens with the potential to provide additional benefits to patients with CF. We have multiple next-generation correctors in the lead-optimization stage of research and expect to begin clinical development of a next-generation corrector in 2015. We hold worldwide development and commercialization rights to ivacaftor, lumacaftor and VX-661.

Our ivacaftor development program for additional indications has received a Breakthrough Therapy designation from the FDA. The FDA also has designated the combination regimens of lumacaftor with ivacaftor and VX-661 with ivacaftor for the treatment of patients with CF who have the F508del mutation on both alleles as Breakthrough Therapies.

KALYDECO (ivacaftor)

KALYDECO (ivacaftor) is an orally-administered CFTR potentiator that is approved in the United States, Australia, Canada and the European Union for the treatment of patients six years of age and older with CF who have specific mutations in their CFTR gene. In the United States, these mutations are G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D and R117H. KALYDECO has received recognition as a significant innovation in drug development. In the press release announcing KALYDECO’s approval, the FDA identified KALYDECO as an excellent example of the promise of personalized medicine and a breakthrough therapy for the CF community, because other existing therapies treat only the symptoms of this genetic disease, while KALYDECO addresses the underlying cause. During development, ivacaftor was granted orphan drug designation in the United States and European Union and Fast-track designation in the United States. We use the brand name KALYDECO only 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 the compound by its scientific (or generic) name ivacaftor.

KALYDECO was initially approved in 2012 in the United States and European Union as a treatment for patients with CF six years of age and older who have the G551D mutation in their CFTR gene. In February 2014, the FDA approved KALYDECO for the treatment of patients with CF six years of age and older who have one of eight other mutations in their CFTR gene, which were studied in our first Phase 3 label-expansion clinical trial for ivacaftor. In July 2014, the European Commission approved KALYDECO for this patient group. In December 2014, the FDA approved KALYDECO for the treatment of patients six years of age and older who have the R117H in their CFTR gene. We believe there are more than 3,100 people with CF six years of age and older in North America, Europe and

Australia who currently are eligible for treatment with KALYDECO.

We have completed a Phase 3 clinical trial to evaluate ivacaftor as a treatment for children with CF two to five years of age with specific gating mutations in their CFTR gene, including the G551D mutation, and have submitted an NDA to the FDA and an MAA line extension application to the EMA based on this clinical trial. The target date for the FDA to complete

its review of this NDA under PDUFA is March 17, 2015. We believe there are approximately 300 children with CF two to five years of age who have gating mutations in North America, Europe and Australia. We also have submitted an MAA variation to the EMA for ivacaftor for patients with CF 18 years of age and older with the R117H mutation in their CFTR gene.

Lumacaftor in Combination with Ivacaftor

Lumacaftor is an orally-administered CFTR corrector drug candidate that we are developing in combination with ivacaftor. In November 2014, we submitted an NDA to the FDA and an MAA to the EMA for lumacaftor in combination with ivacaftor in patients with CF twelve years of age and older who have two copies (homozygous) of the F508del mutation in their CFTR gene. In 2015, we submitted in Canada, and expect to submit in Australia, regulatory applications seeking approval for lumacaftor in combination with ivacaftor. These regulatory applications were based on TRAFFIC and TRANSPORT, two Phase 3 randomized, double-blind, placebo-controlled clinical trials of lumacaftor in combination with ivacaftor. The FDA has granted us priority review of the NDA and the European Committee for Medicinal Products has granted our request for Accelerated Assessment of the MAA. The target date for the FDA to complete its review of the NDA for the combination under PDUFA is July 5, 2015. We believe that there are approximately 22,000 patients with CF twelve years of age and older who have two copies of the F508del mutation in North America, Europe and Australia, including approximately 8,500 in the United States and approximately 12,000 in Europe.

We completed TRAFFIC and TRANSPORT in the second quarter of 2014. The combination treatment groups evaluated lumacaftor dosed at either 600 mg once daily or 400 mg every 12 hours in combination with ivacaftor dosed at 250 mg every 12 hours. 1,108 patients enrolled and received at least one dose of study drug in the two clinical trials. The primary endpoint in each of TRAFFIC and TRANSPORT was the mean absolute change from baseline in percent predicted forced expiratory volume in one second, or $ppFEV_1$, at the end of the 24-week treatment period as assessed by the average change in lung function at Week 16 and at Week 24. All four treatment arms within TRAFFIC and TRANSPORT met their primary endpoint. Additionally, statistically significant mean absolute and relative improvements in lung function were observed for all four treatment groups, both within group and versus placebo, at all time-points within the clinical trials (Weeks 2, 4, 8, 16 and 24). The result of statistical testing is often defined in terms of a “p-value,” with $p<0.05$ generally considered to represent a statistically significant difference. As patients in the clinical trials continued to be treated with their standard CF medicines, improvements observed for patients in the combination treatment arms were in addition to any benefits experienced with the use of other CF medicines. Detailed data from each arm of TRAFFIC and TRANSPORT are provided below:

		TRAFFIC Trial			TRANSPORT Trial		
Change in $ppFEV_1$		Placebo (n=184)	Lumacaftor (600 mg once daily) + Ivacaftor (250 mg q12h) (n=183)	Lumacaftor (400 mg q12h) + Ivacaftor (250 mg q12h) (n=182)	Placebo (n=187)	Lumacaftor (600 mg once daily) + Ivacaftor (250 mg q12h) (n=185)	Lumacaftor (400 mg q12h) + Ivacaftor (250 mg q12h) (n=187)
Mean Absolute	Treatment Difference	N/A	4.0 (p<0.0001)	2.6 (p=0.0003)	N/A	2.6 (p=0.0004)	3.0 (p<0.0001)
Change (percentage points)	Within Group	-0.44 (p=0.4002)	3.6 (p<0.0001)	2.2 (p<0.0001)	-0.15 (p=0.7744)	2.5 (p<0.0001)	2.9 (p<0.0001)
Mean Relative	Treatment Difference	N/A	6.7% (p<0.0001)	4.3% (p=0.0006)	N/A	4.4% (p=0.0007)	5.3% (p<0.0001)
Change (%)	Within Group	-0.34% (p=0.7113)	6.4% (p<0.0001)	4.0% (p<0.0001)	0.0% (p=0.9983)	4.4% (p<0.0001)	5.3% (p<0.0001)

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Within TRAFFIC and TRANSPORT, patients who received the combination regimens experienced a 28 to 43 percent decrease in the rate of pulmonary exacerbations (events of worsening signs and symptoms of the disease requiring treatment with antibiotics) over the 24-week treatment period compared to placebo. Detailed data for all key secondary endpoints from each arm of the clinical trials are provided below:

		TRAFFIC Trial			TRANSPORT Trial		
Key Secondary Endpoints		Placebo (n=184)	Lumacaftor (600 mg once daily) + Ivacaftor (250 mg q12h) (n=183)	Lumacaftor (400 mg q12h) + Ivacaftor (250 mg q12h) (n=182)	Placebo (n=187)	Lumacaftor (600 mg once daily) + Ivacaftor (250 mg q12h) (n=185)	Lumacaftor (400 mg q12h) + Ivacaftor (250 mg q12h) (n=187)
Change in Body Mass Index	Treatment Difference	N/A	+0.16 (p=0.1122)	+0.13 (p=0.1938)	N/A	+0.41 (p<0.0001)	+0.36 (p=0.0001)
	Within Group	+0.19 (p=0.0065)	+0.35 (p<0.0001)	+0.32 (p<0.0001)	+0.07 (p=0.2892)	+0.48 (p<0.0001)	+0.43 (p<0.0001)
Change in CFQ-R	Treatment Difference	N/A	+3.9 (p=0.0168)	+1.5 (p=0.3569)	N/A	+2.2 (p=0.1651)	+2.9 (p=0.0736)
	Within Group	+1.1 (p=0.3423)	+5.0 (p<0.0001)	+2.6 (p=0.0295)	+2.8 (p=0.0152)	+5.0 (p<0.0001)	+5.7 (p<0.0001)
Patients with 5% or Greater Relative Improvement in $ppFEV_1$	%	22%	46%	37%	23%	46%	41%
	Odds Ratio	N/A	2.94 (p<0.0001)	2.06 (p=0.0023)	N/A	2.96 (p<0.0001)	2.38 (p=0.0001)
Number of Pulmonary Exacerbations	Number of Events (rate per 48 weeks)	112 (1.07)	79 (0.77)	73 (0.71)	139 (1.18)	94 (0.82)	79 (0.67)
	Rate Ratio	N/A	0.72 (p=0.0491)	0.66 (p=0.0169)	N/A	0.69 (p=0.0116)	0.57 (p=0.0002)

The combination regimens were generally well tolerated. The most common adverse events, regardless of treatment group, were infective pulmonary exacerbation, cough, headache and increased sputum, and adverse events that occurred more frequently in patients who received the combination regimens than those who received placebo were generally respiratory in nature and included dyspnea and respiration abnormal. 4.2 percent of all patients who received combination therapy, regardless of dosing group, discontinued treatment because of adverse events compared to 1.6 percent of those who received placebo. Across TRAFFIC and TRANSPORT, elevated liver enzymes (greater than three times the upper limit of normal) were observed in 5.2 percent of patients who received combination therapy compared to 5.1 percent of those who received placebo. Seven patients who received combination therapy experienced serious adverse events related to abnormal liver function tests, compared to zero patients who received placebo. Following discontinuation or interruption of the combination treatment, liver function tests returned to baseline for six of the seven patients and the seventh patient's liver function tests improved substantially.

We also plan to initiate a clinical trial of lumacaftor in combination with ivacaftor in children with CF six to eleven years of age who have two copies of the F508del mutation in their CFTR gene in the first half of 2015. This clinical trial is expected to evaluate the combination regimen as part of a single-arm, open-label design in approximately 50 children. The primary endpoint of this clinical trial will be safety and pharmacokinetics.

VX-661 in Combination with Ivacaftor

VX-661 is an orally-administered CFTR corrector drug candidate that we are developing in combination with ivacaftor. We have initiated a Phase 3 development program for VX-661 in combination with ivacaftor in patients with CF twelve years of age and older. The initiation of this Phase 3 development program was based on safety and

efficacy data from Phase 2 clinical trials of VX-661, including interim data from an ongoing 12-week Phase 2 clinical trial and a previously completed clinical trial of VX-661 in combination with ivacaftor in patients with CF who have two copies of the F508del mutation and in patients with CF who have one copy of the F508del mutation and one copy of the G551D mutation, and recent regulatory discussions regarding the design of the Phase 3 development program. This Phase 3 development program is expected to consist of four clinical trials that will evaluate VX-661 as follows:

Two Copies of the F508del Mutation. In 2015, we initiated a Phase 3 clinical trial to evaluate the combination of VX-661 and ivacaftor in patients with CF twelve years of age and older who have two copies of the F508del mutation in their CFTR gene. The primary endpoint of this clinical trial is absolute change in $ppFEV_1$ through six months of treatment for patients who receive the combination treatment versus patients who receive placebo. This clinical trial is expected to enroll approximately 500 patients.

- One Copy of the F508del Mutation and a Second Mutation That Results in a Gating Defect in the CFTR Protein. In the second quarter of 2015, we plan to initiate a Phase 3 clinical trial to evaluate the combination of VX-661 and ivacaftor in patients with CF who have one copy of the F508del mutation in their CFTR gene and a second mutation in their CFTR gene that results in a gating defect in the CFTR protein. The primary endpoint of this clinical trial is expected to be absolute change in $ppFEV_1$ through eight weeks of treatment for patients who receive the combination treatment versus patients who receive ivacaftor alone. This clinical trial is expected to enroll approximately 200 patients.
- One Copy of the F508del Mutation and a Second Mutation That Results in Residual CFTR Function. In the second quarter of 2015, we plan to initiate a Phase 3 clinical trial to evaluate the combination of VX-661 and ivacaftor in patients with CF who have one copy of the F508del mutation in their CFTR gene and a second mutation in their CFTR gene that results in residual CFTR function. This clinical trial also will evaluate ivacaftor dosed without VX-661. The primary endpoint of this clinical trial will be absolute change in $ppFEV_1$ through eight weeks of treatment as part of a crossover design. This clinical trial is expected to enroll approximately 300 patients.
- One Copy of the F508del Mutation and A Second Mutation That Results in Minimal CFTR Function. In the second quarter of 2015, we plan to initiate a Phase 3 clinical trial to evaluate the combination of VX-661 and ivacaftor in 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. This clinical trial is expected initially to enroll approximately 120 patients, and the primary endpoint will be absolute change in $ppFEV_1$ through 12 weeks of treatment for patients who receive the combination treatment versus patients who receive placebo. Expansion of this clinical trial to an additional approximately 150 patients will depend on an interim futility analysis of efficacy data from the initial approximately 120 patients.

HCV INFECTION

INCIVEK (telaprevir) is an orally-administered HCV protease inhibitor for adults with genotype 1 HCV infection that was prescribed in combination with pegylated-interferon and ribavirin. INCIVEK achieved rapid acceptance for the treatment of patients with genotype 1 HCV infection in the United States and accounted for a majority of our net product revenues in 2011, 2012 and 2013. However, INCIVEK revenues declined rapidly after reaching a peak in the fourth quarter of 2011. In 2013, in response to declining sales of INCIVEK and increased competition, we reduced our focus on marketing INCIVEK and eliminated the U.S. field-based sales force that had been promoting INCIVEK. We have withdrawn INCIVEK from the market in the United States, and we expect to wind-down any remaining activities relating to the field of HCV infection in 2015.

Our collaborators, Janssen Pharmaceutica NV and Mitsubishi Tanabe Pharma Corporation, retain fully-paid licenses to telaprevir and currently market telaprevir in their respective territories. In the fourth quarter of 2014, we provided notice of termination of the collaboration with Alios BioPharma, Inc. that related to the development of HCV nucleotide analogues.

RESEARCH AND EARLY-STAGE DEVELOPMENT PROGRAMS

We believe that our integrated drug design approach has significantly enhanced our ability to discover and develop small molecule drug candidates directed at biologically complex targets associated with serious diseases. Our platform integrates genetics, biology, pharmacology, drug metabolism and pharmacokinetics, toxicology, material sciences, biophysics, medicinal chemistry and process chemistry, automation and information technologies in a coordinated fashion throughout the discovery process. We believe that our approach has been validated through our success in moving novel drug candidates into clinical trials and obtaining marketing approvals for KALYDECO and INCIVEK. Currently, the disease areas of highest priority to us from a research perspective are: CF and other genetic diseases; cancer; and neurological diseases and disorders. We focus our research activities on products that would be prescribed

by specialist physicians for the treatment of rare or life-threatening diseases, which are referred to as specialty markets. In CF, our research group is working to identify additional corrector compounds that could be included in future dual- and/or triple-combination treatment regimens that have the

potential to provide additional benefits to patients with CF. We expect to begin clinical development of a next-generation corrector in 2015.

Driven by the disease areas selected, we attempt to identify multiple approaches within each indication that, either as a stand-alone therapy or combination therapy, could provide treatment options that are transformational in nature. We select disease areas by mapping our research strengths onto disease areas with high unmet medical need, with an emphasis on indications, where based on scientific insights, we believe that we, independently or in collaboration with third parties, will be able to discover, develop and commercialize important medicines for serious diseases.

Our drug discovery efforts have produced a variety of drug candidates that have been commercialized or are in preclinical or clinical development. We believe our ongoing research programs will continue to create value for us by generating new drug candidates in areas of significant unmet medical need. For example, in oncology, we are developing VX-803 and VX-970, which are designed to regulate the repair of damaged DNA within cancer cells through inhibition of a protein kinase known as ATR. We believe that ATR inhibition may enhance the efficacy of conventional DNA-damaging agents that are central to the efficacy of numerous established cancer therapies. As a result, we believe that ATR inhibitors could be useful agents in a number of oncology indications either alone or in combination with other drugs. We are evaluating VX-803 and VX-970 in open-label, Phase 1 clinical trials in patients with advanced solid tumors. We expect to initiate clinical development for one or more additional compounds from our research programs in 2015.

To augment our internal research programs, we seek to collaborate with leading academic research institutions, government laboratories, foundations and other organizations in order to advance research in our areas of therapeutic interest as well as in areas of basic technological enablement. We have established relationships with organizations and consortia of organizations from around the world with expertise in areas of interest to us and intend to leverage that experience to further our research efforts.

COMMERCIAL ORGANIZATION

Our commercial organization focuses on supporting sales of KALYDECO in the United States, Europe, Canada and Australia and is preparing to support sales of lumacaftor in combination with ivacaftor. Our sales and marketing organizations are responsible for promoting products to health care providers and obtaining reimbursement for products from third-party payors, including governmental organizations in the United States and non U.S. markets.

Our U.S. field-based CF commercial team includes approximately 20 therapeutic specialists, which we believe will be sufficient to support future needs, including potential sales of lumacaftor in combination with ivacaftor. 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 to promote KALYDECO and will need to increase the size of this sales force moderately as we continue to expand geographically.

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 CFFT in 1998. We entered into the current collaboration agreement with CFFT in 2004 and amended it several times to support research and development activities related to potentiator compounds and corrector compounds, including ivacaftor, lumacaftor and VX-661. Pursuant to an April 2011 amendment to the collaboration agreement, CFFT agreed to provide financial support for development activities for VX-661, a corrector compound discovered under the collaboration, and additional research and development activities directed at discovering new corrector compounds. We retain worldwide rights to develop and commercialize ivacaftor, lumacaftor, VX-661 and any other compounds discovered during the course of the research collaboration with CFFT. We are obligated to pay CFFT tiered royalties ranging from single digits to sub-teens, calculated as a percentage of net sales, on ivacaftor, as well as lumacaftor, VX-661 and compounds discovered during the research terms of the agreement with CFFT, the last of which concluded February 2014. We have made the two commercial milestone payments required under the collaboration agreement upon achievement of certain sales levels of KALYDECO. Under the collaboration agreement, we also are obligated to make a total of two one-time commercial milestone payments upon achievement of certain sales levels for certain CFTR corrector compounds.

For each compound commercialized under this collaboration, we will have royalty obligations to CFFT until the expiration of patents covering that 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 patent applications in the United States and European Union covering the composition-of-matter of lumacaftor that expire in 2026, subject to potential patent life extensions. The collaboration also may be terminated by either party for a material breach by the other, subject to notice and cure provisions.

BioAxone Biosciences, Inc.

In October 2014, we entered into a license and collaboration agreement with BioAxone Biosciences, Inc., or BioAxone, a privately-held biotechnology company. Pursuant to this agreement, we are collaborating with BioAxone on the research, development and commercialization of VX-210 (formerly referred to as Cethrin), a biologic controlled by BioAxone, for the treatment of patients with spinal cord injuries. VX-210 is a Rho inhibitor, also described as a Rho antagonist, which we believe has the potential to block inhibitory signaling, which may result in the regrowth and/or regeneration of axons after spinal injury. VX-210 has been evaluated as a single dose application in an open-label, non-placebo controlled Phase 1/2a clinical trial at multiple doses in 48 patients with thoracic and cervical acute spinal cord injuries. We expect to commence a Phase 2b clinical trial of VX-210 in late 2015.

We paid BioAxone initial payments of $10.0 million and BioAxone has the potential to receive up to $90.0 million in milestones and fees, including development and regulatory milestone payments and a license continuation fee. In addition, BioAxone would receive 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 at the earliest of (a) the day the FDA accepts a 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 may also 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.

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.

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Janssen Pharmaceuticals, Inc.

In 2014, we entered into an agreement with Janssen Pharmaceuticals, Inc., or 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 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.

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 2 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)
KALYDECO (ivacaftor)	Granted (2027)	Granted (2025)
lumacaftor	Application Pending (2026)	Granted (2026)
VX-661	Granted (2027)	Application Pending (2027)

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, our intellectual property holdings include:

- U.S. and foreign patent applications covering potentiator compounds and corrector compounds for the CFTR protein, including ivacaftor, lumacaftor and VX-661 and many other related compounds, and the use of those potentiators and correctors to treat CF.
- U.S. and foreign patents and patent applications covering VX-803 and VX-970 and the use of VX-803 and VX-970 to treat oncology 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 these compounds, including ivacaftor and lumacaftor.

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.

Ivacaftor was granted orphan drug status in the United States and the European Union. 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 are entitled to orphan drug exclusivity for ivacaftor in the United States and the European Union, which means that the FDA may not approve another application to market ivacaftor for the same indication for a period of seven years following approval, and the EMA cannot accept an MAA for a drug similar to ivacaftor for a period of ten years following approval. As a result of the orphan drug exclusivity, even if a competitor successfully challenges the ivacaftor patents, it could not obtain approval from the FDA to market ivacaftor for the treatment of patients with a G551D mutation in their CFTR gene in the United States until 2019, or submit an MAA for the treatment of patients with a G551D mutation in their CFTR gene in the European Union until 2022, except in very limited circumstances.

Lumacaftor, and the fixed dose combination of lumacaftor and ivacaftor were granted orphan drug status in the United States and the European Union. We have a European patent that covers the composition of matter of lumacaftor that we expect will provide intellectual property protection in the European Union through its expiration date in 2026, subject to potential extension. We have pending applications in the United States covering the composition-of-matter of lumacaftor.

VX-661 was granted orphan drug status in the United States and the European Union. We have a United States patent that covers the composition of matter of VX-661 that we expect will provide intellectual property protection in the United States through its expiration date in 2027, subject to potential extension. We have pending applications in the European Union covering the composition-of-matter of VX-661.

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 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 we rely on a sole source supplier of one component of our products and drug candidates.

We expect that we will continue for the foreseeable future to rely on third parties to meet most of our commercial supply needs and some of our clinical supply needs. We are in the process of establishing our own small-scale manufacturing capabilities, which we plan to use for clinical trial supplies and as an additional source for 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, supply us with raw materials, and convert these raw materials into drug substance, and 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 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. A disruption in the clinical supply of ivacaftor could delay the completion of clinical trials and/or affect timelines

for submitting regulatory filings. Our supply chain includes a sole-source manufacturer that has the capability of providing its services to us from multiple sites.

Manufacture of Co-formulated Lumacaftor/Ivacaftor

We have developed several manufacturing processes to produce commercial quantities of co-formulated lumacaftor/ivacaftor, including a process utilizing continuous manufacturing technology as well as a traditional batch manufacturing process. We have established manufacturing capabilities at our third-party manufacturer in the United Kingdom, which was used to produce a portion of the clinical trial supplies for our Phase 3 clinical trials of lumacaftor in combination with ivacaftor, and are in the process of establishing continuous manufacturing capabilities and seeking validation for these capabilities at our facility located in Boston, Massachusetts. The goal of continuous process manufacturing is to reduce material waste and cycle times and improve yield, which may result in reduced cost, reduced development and production timelines, lower inventories and increased market response flexibility. While continuous process manufacturing has been used in many industries, we believe that we are the first company to seek approval for an NDA using a continuous manufacturing process. A third-party manufacturer also is producing commercial quantities of co-formulated lumacaftor/ivacaftor using the traditional batch manufacturing process we designed.

Manufacture of VX-661/Ivacaftor

We expect to use a traditional batch manufacturing process to obtain a supply of VX-661 to be used in our Phase 3 clinical trials of VX-661 in combination with ivacaftor. If we successfully commercial VX-661 in combination with ivacaftor, we plan to produce our commercial supply of VX-661 using a continuous manufacturing process.

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 publicly-traded companies such as Novartis, Pfizer, ProQR Therapeutics B.V., and Genzyme, which is a division of Sanofi, and several private companies. Although we are the first company to successfully develop a drug that treats the underlying cause of CF, KALYDECO is approved to treat only a small percentage of patients with CF. Our competitors have research and development programs directed at identifying and developing CFTR potentiators, CFTR correctors and drug candidates with other mechanisms of action that seek to address the underlying cause of CF, and our success in rapidly developing and commercializing KALYDECO (ivacaftor) and developing and potentially commercializing lumacaftor in combination with ivacaftor may increase the resources that our competitors allocate to the development of these potential treatments for CF. If one or more competing therapies are successfully developed as a treatment for patients with CF, our revenues from KALYDECO, lumacaftor in combination with ivacaftor, and/or our other CF drug candidates, if then approved, could face significant competitive pressure.

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GOVERNMENT REGULATION

The research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, safety monitoring, record keeping, promotion, advertising, distribution and marketing of our products and drug candidates are subject to extensive regulation by United States and foreign governmental authorities.

United States Government Regulation

New Drug Application Approval Processes

In the United States, the FDA regulates drugs under the Federal Food, Drug and Cosmetic Act, or the FDCA, and implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with applicable federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources. 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 to administrative or judicial sanctions, any of which could have a material adverse effect on us. These sanctions could include:

- refusal to approve or delay in review of pending applications;
- withdrawal of an approval or the implementation of limitations on a previously approved indication for use;
- imposition of a clinical hold, a risk mitigation and evaluation strategy or other safety-related limitations;
- warning letters or “untitled letters”;
- product seizures;
- total or partial suspension of production or distribution; or
- injunctions, fines, disgorgement, or civil or criminal penalties.

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 investigational new drug, or 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 to assure that the facilities, methods and controls are adequate to preserve the product’s identity, strength, quality and purity; 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. Preclinical or nonclinical testing typically continues even after the IND is submitted. In addition to including the results of the preclinical studies, the IND also will include a protocol detailing, among other things, the objectives of the initial clinical trial and the parameters to be used in monitoring safety. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, places the IND on clinical hold. If an IND is placed on clinical hold, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin. A clinical hold may occur at any time during the life of an IND, and may affect one or more specific clinical trials or all clinical trials conducted under the IND.

All clinical trials must be conducted under the supervision of one or more qualified investigators in accordance with GCP. They must be conducted under protocols detailing the objectives of the trial, dosing procedures, subject selection and exclusion criteria and the safety and effectiveness criteria to be evaluated. Each protocol and any amendments must be submitted to the FDA as part of the IND, and 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. An institutional review board, or IRB, at each institution participating in the clinical trial must review and approve the protocol and any amendments before a clinical trial commences or continues at that institution, approve the information regarding the clinical trial and the consent form that must be provided to each trial subject or his or her legal representative, and monitor the clinical trial until completed and otherwise comply with IRB regulations.

Clinical trials typically are conducted in three sequential phases that may overlap or be combined:

- 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. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug candidate has been associated with unexpected serious harm to healthy volunteers or patients.

We estimate that it generally takes 10 to 15 years, or possibly longer, to discover, develop and bring to market a new pharmaceutical product in the United States, as outlined below:

Phase	Estimated Duration
Discovery	2 to 4 years
Preclinical	1 to 2 years
Phase 1	1 to 2 years
Phase 2	2 to 4 years
Phase 3	2 to 4 years
FDA approval	6 months to 2 years

During the development of a new drug, sponsors are given opportunities to meet with the FDA at certain points. These points may be prior to submission of an IND, at the end of Phase 2 testing, and before an NDA is submitted. Meetings at other times may be requested. These meetings can provide an opportunity for the sponsor to share information about the data gathered to date, for the FDA to provide advice, and for the sponsor and FDA to reach agreement on the next phase of development. Sponsors typically use the end of Phase 2 meeting to discuss their Phase 2 clinical results and present their plans for the pivotal Phase 3 clinical trial that they believe will support approval of the drug candidate.

As part of the development process, companies usually complete animal safety studies and also must develop additional information about the chemistry and physical characteristics of the drug and finalize a process for manufacturing the product in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate, and the manufacturer must develop methods for testing the quality, purity and potency of the final products. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable

deterioration over its shelf-life.

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 may not approve an NDA if the applicable regulatory criteria are not satisfied or may require additional clinical or other data. Even if such data are submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. 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.

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. The complete response letter usually describes all of the specific deficiencies in the NDA identified by the FDA. If a complete response letter is issued, the applicant may either resubmit the NDA, addressing all of the deficiencies identified in the letter, or withdraw the application.

Expedited Review and Approval

The FDA has various programs, including Fast Track, priority review, and accelerated approval, that are intended to expedite or simplify the process for reviewing drug candidates, and/or provide for approval on the basis of surrogate endpoints. Even if a drug candidate qualifies for one or more of these programs, the FDA may later decide that the drug candidate no longer meets the conditions for qualification or that the time period for FDA review or approval will not be shortened. Generally, drug candidates that may be eligible for these programs are those for serious or life-threatening conditions, those with the potential to address unmet medical needs, and those that offer meaningful benefits over existing treatments. For example, Fast Track is a process designed to facilitate the development, and expedite the review of drug candidates to treat serious diseases and fill an unmet medical need. Priority review is designed to give drug candidates that offer major advances in treatment or provide a treatment where no adequate therapy exists an initial review within six months as compared to a standard review time of ten months. Although Fast Track and priority review do not affect the standards for approval, the FDA will attempt to facilitate early and frequent meetings with a sponsor of a Fast Track designated drug candidate and expedite review of the application for a drug candidate designated for priority review. Accelerated approval provides an earlier approval of drugs that treat serious diseases, and that fill an unmet medical need based on a surrogate endpoint, which is a laboratory measurement or physical sign used as an indirect or substitute measurement representing a clinically meaningful outcome. As a condition of approval, the FDA may require that a sponsor of a product receiving accelerated approval perform post-marketing clinical trials.

In July 2012, the Food and Drug Administration Safety and Innovation Act, or FDASIA, was enacted, amending the FDCA. As part of FDASIA, Congress created a drug designation called "Breakthrough Therapy." This designation is intended to facilitate expedited development and review of a compound which, alone or in combination with one or more other compounds, is intended to treat a serious or life-threatening disease or condition and for which preliminary clinical evidence indicates that the compound may demonstrate substantial clinical improvement over existing therapies. Breakthrough Therapy designation may be requested at the filing of, or as an amendment to, an IND based on criteria established by the FDA.

Actions identified in FDASIA that may expedite the development and review of a Breakthrough Therapy include, as appropriate: holding meetings with the sponsor and the review team throughout the development of the drug; involving senior managers and experienced review staff, as appropriate, in a collaborative, cross-disciplinary review;

and assigning a cross-disciplinary project lead for the FDA review team to facilitate efficient review of the development program and serve as a scientific liaison between the review team and the sponsor. We expect that over time the FDA will develop regulations and/or provide additional guidance regarding the development of drug candidates that receive Breakthrough Therapy designation.

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.

Drug manufacturers and other entities involved in the manufacture and distribution of approved products are required to register with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and some state agencies for compliance with cGMP and other laws.

We rely, and expect to continue to rely, on third parties for the production of our products. Future FDA and state 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.

From time to time, new legislation is enacted that changes the statutory provisions governing the approval, manufacturing and marketing of products regulated by the FDA. 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 changed.

Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of FDA approval of the use of our drugs, some of our United States patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND, and the submission date of an NDA, plus the time between the submission date of an NDA and the approval of that application. Only one patent applicable to an approved product is eligible for the extension and the extension must be applied for prior to expiration of the patent. The United States Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may apply for restorations of patent term for some of our currently owned or licensed patents to add patent life beyond their current expiration date, depending on the expected length of clinical trials and other factors involved in the submission of the relevant NDA.

Market exclusivity provisions under the FDCA also can delay the submission or the approval of certain applications. The FDCA provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant to

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gain approval of an NDA for a new chemical entity. For a new chemical entity that qualifies for Orphan Drug designation, the FDCA provides such marketing exclusivity for a period of seven years. A product is a new chemical entity if the FDA has not previously approved any other new product containing the same active moiety, which is the molecule responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application, or ANDA, or a 505(b)(2) NDA submitted by another company for another version of such product where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement. The FDCA also provides three years of marketing exclusivity for an NDA, 505(b)(2) NDA or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example, for new indications, dosages, or strengths of an existing drug. This three-year exclusivity covers only the conditions associated with the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the original active agent.

Pediatric Exclusivity

Section 505A of the FDCA, as amended by the FDA Amendments Act of 2007, permits certain drugs to obtain an additional six months of exclusivity, if the sponsor submits information requested in writing by the FDA, or a written request, relating to the use of the drug in children. The FDA may not issue a written request for clinical trials on unapproved or approved indications or where it determines that information relating to the use of a drug in a pediatric population, or part of the pediatric population, may not produce health benefits in that population.

Foreign Regulation

In addition to regulations in the United States, we are subject to a variety of foreign regulations governing clinical trials and commercial sales and distribution of our products. 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. The decentralized procedure provides for approval by one or more "concerned" member states based on an assessment of an application performed by one member state, known as the "reference" member state. Under the decentralized approval procedure, an applicant submits an application, or dossier, and related materials to the reference member state and concerned member states. The reference member state prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. Within 90 days of receiving the reference member state's assessment report, each concerned member state must decide whether or not to approve the assessment report and related materials. If a member state does not recognize the marketing authorization, the disputed points are eventually referred to the European Commission, whose decision is binding on all member states.

Orphan Drug Designation

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, or more than 200,000 people in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for this type of disease or condition will be recovered from sales in the United States for that drug. Orphan drug designation must be requested before submitting an NDA. After the FDA grants orphan drug designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in or shorten the duration of the regulatory review and approval process. KALYDECO and lumacaftor 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, except in very limited circumstances, for

seven years. 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.

As in the United States, we may apply for designation of a drug candidate as an orphan drug for the treatment of a specific indication in the European Union before the application for marketing authorization is made. Orphan drugs in Europe enjoy economic and marketing benefits, including up to 10 years of market exclusivity for the approved indication unless another applicant can show that its product is safer, more effective or otherwise clinically superior to the orphan-designated product.

The FDA and foreign regulators expect holders of exclusivity for orphan drugs, such as KALYDECO, to ensure the availability of sufficient quantities of their orphan drugs to meet the needs of patients. Failure to do so could result in the withdrawal of marketing exclusivity for the orphan drug.

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 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. A plan for the research will 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 will be made to the U.S. Congress. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, it is not clear what effect, if any, the research will have on the sales of our products. It is possible that comparative effectiveness research demonstrating benefits of a competitor's product could adversely affect the sales of our products. If third-party payors do not consider our products to be cost-effective compared to other available therapies, they may not cover our products as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act of 2010, which is referred to as the ACA, was enacted in March 2010 and is 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. Our rebates associated with the Medicare Part D "donut hole" have not been significant. In 2014, 2013 and 2012, we recorded $10.7 million, $10.4 million and $1.8 million, respectively, in sales, general and administrative expenses related to the branded prescription drug fee established pursuant to the ACA. We were not subject to this fee prior to 2012. The branded prescription drug fee is not tax deductible. We cannot predict all of the effects of the ACA on pharmaceutical companies as many of the ACA reforms require the promulgation of detailed regulations implementing the statutory provisions, which has not yet occurred.

In Europe and many other foreign countries, the success of KALYDECO and of lumacaftor in combination with ivacaftor, if approved, 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 begin while the reimbursement rate that a company will receive in future periods 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 European Union provides options for its member states to restrict the range of drugs for which their national health insurance systems provide reimbursement and to 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 allow favorable reimbursement and pricing arrangements for any of our products.

Other United States Regulations

Pharmaceutical companies also are subject to various federal and state laws pertaining to health care "fraud and abuse," including anti-kickback laws and false claims laws, and the reporting of payments to physicians and teaching hospitals.

Anti-kickback Laws

U.S. federal laws prohibit fraud and abuse involving state and federal health care programs, such as Medicare and Medicaid. These laws are interpreted broadly and enforced aggressively by various state and federal agencies, including the Centers for Medicare & Medicaid Services, or CMS, the Department of Justice, the Office of Inspector General for HHS and various state agencies. These anti-kickback laws prohibit, among other things, knowingly and willfully offering, paying, soliciting, receiving or providing remuneration, directly or indirectly, in exchange for or to induce either the referral of an individual, or the furnishing, arranging for or recommending of an item or service that is reimbursable, in whole or in part, by a federal health care program. Remuneration is broadly defined to include anything of value, such as, cash payments, gifts or gift certificates, discounts, or the furnishing of services, supplies or equipment. The anti-kickback laws are broad and prohibit many arrangements and practices that are lawful in businesses outside of the health care industry.

The penalties for violating the anti-kickback laws can be severe. The sanctions include criminal and civil penalties, and possible exclusion from the federal health care programs. Many states have adopted laws similar to the federal anti-kickback laws, and some apply to items and services reimbursable by any payor, including third-party payors.

State and Federal Prohibitions on False Claims

The federal False Claims Act imposes liability on any person or entity that, among other things, knowingly presents, or causes to be presented, a false or fraudulent claim for payment to the federal government. Under the False Claims Act, a person acts knowingly if he has actual knowledge of the information or acts in deliberate ignorance or in reckless disregard of the truth or falsity of the information. Specific intent to defraud is not required. Provisions of the False Claims Act allow a private individual to bring an action on behalf of the federal government and to share in any amounts paid by the defendant to the government in connection with the action. The number of filings under these provisions has increased significantly in recent years. When an entity is determined to have violated the False Claims Act, it may be required to pay up to three times the actual damages sustained by the government, plus civil penalties for each false claim. Conduct that violates the False Claims Act may also lead to exclusion from the federal health care programs. Given the number of claims likely to be at issue, potential damages under the False Claims Act for even a single inappropriate arrangement could be significant. In addition, various states have enacted similar laws modeled after the False Claims Act that apply to items and services reimbursed under Medicaid and other state health care programs, and, in several states, such laws apply to claims submitted to all payors.

Federal Prohibitions on Health Care Fraud and False Statements Related to Health Care Matters

Under the administrative simplification provisions of the Health Insurance Portability and Accountability Act of 1996, or HIPAA, and state laws there are numerous regulations for protecting the privacy and security of protected health information. Additional administrative simplification provisions created the following federal crimes: health care fraud, false statements relating to health care matters, theft or embezzlement in connection with a health benefit program and obstruction of criminal investigation of health care offenses. The health care fraud statute prohibits knowingly and willfully executing a scheme to defraud any health care benefit program, including a private insurer. The false statements statute prohibits knowingly and willfully falsifying, concealing, or covering up a material fact or making any materially false, fictitious, or fraudulent statement in connection with the delivery of or payment for health care benefits, items, or services. The theft or embezzlement statute prohibits knowingly and willfully embezzling, stealing or otherwise converting or misapplying the money or property of a health care benefit program. The obstruction of criminal investigations of health care offenses statute prohibits willfully preventing, obstructing, misleading or delaying the communication of information and records relating to a violation of a federal health care offense to a criminal investigator. A violation of any of these laws is a felony and may result in fines, or exclusion from the federal health care programs.

Physician Payment Sunshine Act

The Physician Payment Sunshine Act will require pharmaceutical manufacturers to report annually to the Secretary of HHS payments or other transfers of value made by that entity to physicians and teaching hospitals. In February 2013, regulations were released that contain detailed guidance regarding the information that must be collected and reported. We were required to collect information regarding such payments starting in August 2013 and will be required to begin reporting such information in March 2014. Over the next several years, we will need to continue to dedicate significant resources to enhance our systems and processes in order to comply with these regulations. Failure to comply with the reporting requirements would result in significant civil monetary penalties. Similar laws have been enacted or are under consideration in foreign jurisdictions, including France which has adopted the Loi Bertrand, or French Sunshine Act, which became effective in 2013.

The Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act prohibits U.S. companies and their representatives from offering, promising, authorizing or making payments to foreign officials for the purpose of obtaining or retaining business abroad. In many countries, the health care professionals we regularly interact with may meet the definition of a foreign government official for purposes of the Foreign Corrupt Practices Act.

Other Regulations

In addition to the statutes and regulations described above, we also are subject to regulation in the United States under the Occupational Safety and Health Act, the Environmental Protection Act, the Toxic Substances Control Act, the Resource Conservation and Recovery Act and other federal, state, local and foreign statutes and regulations, now or hereafter in effect.

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EMPLOYEES

As of December 31, 2014, we had approximately 1,830 employees, which was approximately the same number of employees that we had on December 31, 2013. Of these employees, approximately 1,540 were based in the United States, approximately 220 were based in Europe and approximately 70 were based in Canada. Our scientific staff members have diversified experience and expertise in molecular and cell biology, biochemistry, synthetic organic chemistry, protein X-ray crystallography, protein nuclear magnetic resonance spectroscopy, microbiology, computational chemistry, 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 in France and Spain. Science magazine named Vertex as one of its top employers in the life sciences in each of the last five years. 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 Alios as of December 31, 2014 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.	59	Chairman of the Board, Chief Executive Officer and President
David Altshuler, M.D., Ph.D.	50	Executive Vice President, Global Research and Chief Scientific Officer
Stuart A. Arbuckle	49	Executive Vice President and Chief Commercial Officer
Jeffrey A. Chodakewitz, M.D.	59	Executive Vice President, Global Medicines Development and Medical Affairs, and Chief Medical Officer
Amit K. Sachdev, J.D.	47	Executive Vice President, Global Government Strategy, Market Access and Value
Ian F. Smith	49	Executive Vice President and Chief Financial Officer
Paul M. Silva	48	Senior Vice President and Corporate Controller
Joshua S. Boger, Ph.D.	63	Director
Terrence C. Kearney	60	Director
Yuchun Lee	49	Director
Margaret G. McGlynn	55	Director
Wayne J. Riley, M.D.	55	Director
Bruce I. Sachs	55	Director
Elaine S. Ullian	67	Director
William Young	70	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 Harva