VERTEX PHARMACEUTICALS INC / MA
Form 10-K
March 01, 2013
Table of Contents

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, 2012

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.)
130 Waverly Street, Cambridge, Massachusetts	02139-4242
(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 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 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 29, 2012 (the last trading day of the registrant's second fiscal quarter of 2012) was $11.9 billion. As of February 15, 2013, the registrant had 218,188,628 shares of common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the definitive Proxy Statement for the 2013 Annual Meeting of Shareholders to be held on May 8, 2013 are incorporated by reference into Part III of this Annual Report on Form 10-K.

Table of Contents

VERTEX PHARMACEUTICALS INCORPORATED
ANNUAL REPORT ON FORM 10-K
TABLE OF CONTENTS

"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.

Table of Contents

PART I

ITEM 1. BUSINESS

OVERVIEW

We are in the business of discovering, developing, manufacturing and commercializing small molecule drugs for patients with serious diseases. Over the last two years, we have obtained approval for, and initiated commercial sales of, our first two products: INCIVEK (telaprevir), which we market in the United States and Canada for the treatment of adults with genotype 1 hepatitis C virus, or HCV, infection; and KALYDECO (ivacaftor), which we market in the United States, Canada and Europe for the treatment of patients six years of age and older with cystic fibrosis, or CF, who have a specific genetic mutation that is referred to as the G551D mutation. We receive royalties from sales in Europe and other countries of telaprevir, which is marketed as INCIVO, by our collaborator, Janssen Pharmaceutica, N.V.

We invest in scientific innovation to create transformative medicines for patients with serious diseases, with a focus on specialty markets. Our strategy is to make focused investments to invent and develop innovative drugs, while we continue to market INCIVEK and KALYDECO to eligible patients to generate revenues and maintain a strong financial position. In the near term, we plan to focus most of our drug development investment on the following key programs:

Cystic Fibrosis - Our goal is to develop treatment regimens that will provide benefits to as many patients with CF as possible and to maximize those benefits. We are conducting three Phase 3 label-expansion clinical trials and a proof-of-concept clinical trial of ivacaftor monotherapy in people with certain mutations in their cystic fibrosis transmembrane conductance regulator, or CFTR, gene that were not studied in prior Phase 3 clinical trials. If we are able to establish that these additional patient groups will benefit from ivacaftor monotherapy, there is the potential to increase the number of patients eligible for treatment with ivacaftor monotherapy to more than 10% of patients with CF. In February 2013, we initiated an international pivotal Phase 3 development program to evaluate combinations of ivacaftor and our investigational CF corrector VX-809 (lumacaftor) for patients with the most prevalent genetic mutation that causes CF. We plan to conduct two 24-week Phase 3 clinical trials to support the approval of the combination of VX-809 and ivacaftor in patients 12 years of age and older with CF who have two copies of the F508del mutation in the CFTR gene. We expect to obtain final, 24-week safety and efficacy data from both clinical trials in 2014. If these trials are successful, we plan to submit a New Drug Application to the U.S. Food and Drug Administration in 2014 and a Marketing Authorization Application to the European Medicines Agency. We also plan to conduct an 8-week exploratory Phase 2 clinical trial of VX-809 in combination with ivacaftor in patients with CF who are 12 years of age and older and who have one copy of the F508del mutation in the CFTR gene and a pharmacokinetics and safety clinical trial to evaluate VX-809 in combination with ivacaftor in children with CF six to eleven years of age who have two copies of the F508del mutation. If successful, we plan to use the data from the pharmacokinetics and safety clinical trial, along with data from the two Phase 3 clinical trials, for registration in the United States in patients six to eleven years of age, following registration in patients 12 years of age and older, and are continuing discussions with European regulatory agencies for patients in this age group.

HCV - We are investigating all-oral, interferon-free treatment regimens that are 12 weeks or less in duration with a goal of providing a high viral cure rate and improved tolerability, in order to be commercially competitive in the HCV market of the future. We plan to conduct multiple Phase 2 clinical trials to evaluate all-oral combination treatment regimens that include our HCV nucleotide analogue VX-135 together with molecules that have potentially complimentary mechanisms, such as ribavirin, HCV protease inhibitors, HCV NS5A inhibitors and non-nucleoside HCV polymerase inhibitors.

Autoimmune Diseases - We are evaluating our JAK3 inhibitor, VX-509, in a Phase 2 clinical trial that we expect to enroll approximately 350 patients with rheumatoid arthritis.

We may seek collaborators for some of our drug candidates in order to diversify risk, broaden or accelerate or otherwise benefit a development program in an effort to fully-realize the value of a drug candidate.

We plan to continue investing in our research programs and supporting scientific innovation in order to identify and develop transformative medicines. We believe that pursuing research in diverse areas allows us to balance the risks

inherent in drug development and may provide the drug candidates that will form our pipeline in future years. We have later-stage research programs in the areas of cystic fibrosis, Huntington's disease, multiple sclerosis and cancer.

Table of Contents

OUR PRODUCTS

Product	Indication	Mechanism	Markets	Marketing Rights
INCIVEK (telaprevir)	HCV Infection (genotype 1)	HCV Protease Inhibitor	United States and Canada	Vertex
KALYDECO (ivacaftor)	CF (G551D mutation)	CFTR Potentiator	United States, Canada and Europe	Vertex
INCIVO (telaprevir)	HCV Infection (genotype 1)	HCV Protease Inhibitor	Europe and other countries in Janssen's territories	Janssen
TELAVIC (telaprevir)	HCV Infection (genotype 1)	HCV Protease Inhibitor	Japan	Mitsubishi Tanabe

INCIVEK (telaprevir) is an orally-administered HCV protease inhibitor for adults with genotype 1 HCV infection that is prescribed in combination with pegylated-interferon, or peg-IFN, and ribavirin, or RBV. INCIVEK was approved by the U.S. Food and Drug Administration, or FDA, in the second quarter of 2011 and by Health Canada in the third quarter of 2011. In the third quarter of 2011, our collaborators, Janssen Pharmaceutica, N.V., referred to collectively with its affiliates as Janssen, and Mitsubishi Tanabe Pharma Corporation, or Mitsubishi Tanabe, obtained marketing approval for telaprevir from the European Commission and the Japanese Ministry of Health, Labor and Welfare, respectively. Janssen markets telaprevir under the brand name INCIVO in Europe and other countries in its territories, and Mitsubishi Tanabe markets telaprevir under the brand name TELAVIC in Japan. INCIVEK achieved rapid acceptance for the treatment of patients with genotype 1 HCV infection in the United States and was the principle driver of the increase of our total revenues from $143.4 million in 2010 to $1.5 billion in 2012. However, competitive treatment regimens are being developed in late-stage clinical trials for which there have been reported improved viral cure rates and/or tolerability over currently-available regimens, and, as the market has anticipated the approval of these newer regimens, INCIVEK revenues have been declining since reaching a peak in the fourth quarter of 2011. We expect that INCIVEK revenues will continue to decline, and that, as a consequence, our total revenues will decline in 2013 as compared to 2012.

KALYDECO (ivacaftor) is an orally-administered CFTR potentiator that is approved in the United States, Canada and the European Union for the treatment of patients six years of age and older with CF who have at least one copy of the G551D mutation in the CFTR gene. KALYDECO was approved by the FDA in the first quarter of 2012, by the European Commission in the third quarter of 2012 and by Health Canada in the fourth quarter of 2012. We use the brand name KALYDECO only when we refer to the product that has been approved and with respect to the indication(s) on the approved label. Otherwise, we refer to the compound by its scientific (or generic) name ivacaftor, including in discussions of our CF development programs. KALYDECO achieved rapid acceptance in the United States after it was approved, and we expect that our revenues from KALYDECO sales will increase as the product is approved and reimbursed in additional countries in the future.

OUR DRUG CANDIDATES

Drug Candidate	Mechanism	Development Stage
Cystic Fibrosis		
ivacaftor (monotherapy - label expansion trials)	CFTR potentiator	Phase 3
VX-809 (in combination with ivacaftor)	CFTR corrector	Phase 3
VX-661 (in combination with ivacaftor)	CFTR corrector	Phase 2
HCV Infection		
VX-135 (ALS-2200)	HCV nucleotide analogue	Phase 2
VX-222	Non-nucleoside HCV polymerase inhibitor	Phase 2
Autoimmune Diseases		
VX-509	JAK3 inhibitor	Phase 2

Influenza		
VX-787	Influenza virus inhibitor	Phase 2

2

Table of Contents

CYSTIC FIBROSIS

Background

Cystic fibrosis is a rare, life-threatening genetic disease affecting approximately 70,000 people worldwide, including approximately 30,000 people in the United States and approximately 35,000 people in Europe. CF is caused by a defective or missing CFTR protein resulting from mutations in the CFTR gene. Children must inherit two defective CFTR genes, which are referred to as alleles - one from each parent - to have CF. There are more than 1,800 known mutations in the CFTR gene, including two of the most prevalent mutations, the G551D mutation and the F508del mutation.

The G551D mutation results in a “gating” defect in which the defective CFTR protein reaches the cell surface but does not efficiently transport chloride ions across the cell membrane. The F508del mutation results in a “trafficking” defect, in which the CFTR protein does not reach the cell surface 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. CFTR correctors, such as VX-809 and VX-661, are believed to help CFTR protein reach the cell surface. Ivacaftor, known as a CFTR potentiator, keeps the CFTR protein channels on the cell surface open longer to increase the flow of salt and water into and out of the cell.

Based on the 2011 Cystic Fibrosis Foundation Patient Registry Annual Data Report, we estimate that in the United States:

Mutation in CFTR Gene	Approximate Percentage of Patients with CF in the U.S.
G551D mutation on at least one allele	4%
non-G551D gating mutation on at least one allele	1%
R117H mutation on at least one allele	3%
F508del mutation on both alleles (homozygous)	47%
F508del mutation on one allele but not both alleles (heterozygous)	40%

We believe that in Europe there are approximately 900-1,000 patients with CF who have the G551D mutation on at least one allele and that more than 40% of patients with CF in Europe have the F508del mutation on both alleles.

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. We discovered ivacaftor, VX-809 and VX-661 in our research collaboration with the Cystic Fibrosis Foundation Therapeutics Incorporated, or CFFT. Pursuant to our collaboration with CFFT, 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 that have the potential to provide additional benefits to patients with CF. We hold worldwide development and commercialization rights to ivacaftor, VX-809 and VX-661. We pay royalties to CFFT on net sales of ivacaftor and will pay royalties to CFFT on any net sales of VX-809 and VX-661, if they are approved.

KALYDECO (ivacaftor)

KALYDECO (ivacaftor) is an orally-administered CFTR potentiator approved in the United States, the European Union and Canada for the treatment of patients six years of age and older with CF who have the G551D mutation on at least one allele. We also have submitted an application for approval of ivacaftor in Australia. 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. The Wall Street Journal named KALYDECO as the winner of its 2012 Technology Innovation award in the Medicine and Biotech category.

During development, ivacaftor was granted orphan drug designation in the United States and European Union and Fast-track designation in the United States and, due to its promise, was advanced rapidly through development. In 2008, we

3

Table of Contents

evaluated ivacaftor in a small Phase 2a clinical trial that enrolled 39 patients with CF who had the G551D mutation on at least one allele. Based on the safety and efficacy data from this clinical trial, we moved directly into a Phase 3 clinical program, which we initiated in May 2009 and completed in mid-2011. We filed for approval to market ivacaftor in the United States in November 2011 and obtained approval from the FDA in January 2012, which was more than two months ahead of the original target date that had been established by the FDA. We also obtained rapid approval for ivacaftor in the European Union and Canada later in 2012.

Since KALYDECO's approval in the first quarter of 2012, most eligible patients in the United States have initiated and are receiving treatment with KALYDECO. We are in discussions regarding reimbursement for KALYDECO in multiple international markets. In France and Germany, we began commercial sales of KALYDECO in 2012, but we are continuing to discuss the reimbursement rate we will receive for KALYDECO in future periods. Funding for KALYDECO has been recommended in England and Ireland, and we anticipate that reimbursement in these countries will begin in the second quarter of 2013. In other countries, we must first complete the reimbursement discussions before we commence commercial sales.

CF Drug Development Programs

We are continuing our work in CF to develop treatment regimens that will provide benefits to as many patients with CF as possible and to maximize those benefits. We are seeking to increase the number of patients with CF who could benefit from our medicines both by evaluating ivacaftor monotherapy in patient groups who may benefit from monotherapy but that were not evaluated in our earlier clinical trials, and by evaluating combinations of ivacaftor with our investigational corrector compounds, VX-809 and VX-661, in patients with the most prevalent form of CF, those with the F508del mutation. Our ivacaftor monotherapy development program for additional indications has received a Breakthrough Therapy designation from the FDA. The FDA also has designated the combination regimen of VX-809 with ivacaftor for the treatment of patients with CF who have the F508del mutation on both alleles as a Breakthrough Therapy. Our two programs were the first to receive Breakthrough Therapy designations from the FDA under the 2012 Food and Drug Administration Safety and Innovation Act. See page 22 for a discussion of Breakthrough Therapy designation.

Ivacaftor (monotherapy)

Ivacaftor monotherapy is approved (as KALYDECO) as a treatment for patients six years of age and older with CF who have the G551D mutation on at least one allele, which represents a small percentage of patients with CF. We believe that ivacaftor monotherapy also may be effective as a treatment for patients with CF who have non-G551D gating mutations on at least one allele, patients with CF who have the R117H mutation on at least one allele and patients who have clinical or laboratory evidence of residual CFTR protein function. We also are developing a pediatric formulation of ivacaftor that could be used to treat children two to five years of age. If we are able to establish that these additional patient groups will benefit from ivacaftor monotherapy, there is the potential to increase the number of patients eligible for treatment with ivacaftor monotherapy to more than 10% of patients with CF.

We are conducting three Phase 3 label-expansion clinical trials and a Phase 2 clinical trial of ivacaftor monotherapy:

- We have completed enrollment in a Phase 3 clinical trial evaluating ivacaftor in patients six years of age and older with CF with gating mutations other than the G551D mutation.
- We are continuing enrollment in a Phase 3 clinical trial evaluating ivacaftor in patients six years of age and older with CF with the R117H mutation in the CFTR gene on at least one allele.
- We have begun dosing patients in a Phase 3 clinical trial in which we are evaluating a pediatric formulation of ivacaftor as a treatment for children two to five years of age with gating mutations in the CFTR gene, including the G551D mutation.
- We are enrolling patients in a Phase 2 clinical trial in which we are evaluating ivacaftor in patients with CF who have clinical evidence of residual CFTR function.

We expect to obtain data from the Phase 3 clinical trials evaluating patients six years of age and older in 2013. We are discussing with the FDA how the Breakthrough Therapy designation may affect the timing and content of regulatory submissions in the United States to support expansion of the ivacaftor label.

4

Table of Contents

VX-809 in Combination with Ivacaftor

In February 2013, we initiated an international pivotal Phase 3 clinical program to evaluate combinations of VX-809 and ivacaftor in patients with CF who are homozygous (a copy on both genes) with the F508del mutation in their CFTR gene. We plan to conduct two 24-week Phase 3 clinical trials designed to support approval of the combination of VX-809 and ivacaftor for patients with CF 12 years of age and older. We expect to obtain final 24-week safety and efficacy data from both of these Phase 3 clinical trials in 2014. If these trials are successful, we plan to submit a New Drug Application, or NDA, to the FDA in 2014 and a Marketing Authorization Application to the European Medicines Agency.

The two 24-week, randomized, double-blind, placebo-controlled Phase 3 clinical trials are known as TRAFFIC and TRANSPORT. Each Phase 3 clinical trial will enroll approximately 500 patients with CF who are homozygous for the F508del mutation, for a total of approximately 1,000 patients. The two clinical trials have the same design and together will be conducted at approximately 200 clinical trial sites in North America, Europe and Australia. Each clinical trial will include two 24-week combination treatment arms and one 24-week placebo arm. The treatment arms will evaluate two treatment regimens of VX-809 (600mg once-daily (QD) and 400mg every twelve hours (q12h)) in combination with ivacaftor (250mg every twelve hours (q12h)). Fixed-dose tablets that contain both VX-809 and ivacaftor or placebo will be used in both clinical trials. The initial 24-week treatment period will be followed with a separate rollover double-blind extension clinical trial where all eligible patients, including those who received placebo, will receive one of the combination treatment regimens for up to an additional 96 weeks.

The primary endpoint of each Phase 3 clinical trial is relative improvement in lung function (percent predicted FEV_1) through 24 weeks of treatment compared to placebo. Safety and tolerability also will be assessed through 24 weeks. Key secondary endpoints include absolute improvement in FEV_1, change in body mass index (BMI) or weight gain, number of pulmonary exacerbations, and improvements in patient-reported outcomes as measured by the CF Questionnaire Revised (CFQ-R), among others.

We also plan to conduct a clinical trial of VX-809 in combination with ivacaftor in patients with CF six to eleven years of age who are homozygous for the F508del mutation. This clinical trial will evaluate the pharmacokinetics and safety of VX-809 in combination with ivacaftor for up to 24 weeks. If successful, we plan to use the data from this clinical trial, along with data from the two Phase 3 clinical trials, for registration in the United States in patients six to eleven years of age, following registration in patients 12 years of age and older, and are continuing discussions with European regulatory agencies for patients in this age group.

The design of the Phase 3 clinical program was supported by data from a Phase 2 clinical trial of VX-809 in combination with ivacaftor. The two combination dosing regimens we selected for evaluation in Phase 3 clinical trials were evaluated in separate parts of this Phase 2 clinical trial referred to as Cohort 2 and Cohort 3.

- Cohort 2 - We evaluated the 600mg once-daily (QD) dose of VX-809 in combination with ivacaftor (250mg q12h) in Cohort 2 in 21 patients with CF who are homozygous for the F508del mutation. This regimen resulted in statistically significant improvements in lung function (within group and versus placebo) during the combination dosing period, as set forth in the following table:

		Mean Absolute and Relative Changes in Percent Predicted FEV_1		
		Day 0 - 28; VX-809 Alone	Day 28 - 56; VX-809 + ivacaftor	Day 0 - 56
VX-809 (600mg QD) + ivacaftor (250mg q12h)	Within Group			
	Absolute	-2.9 (p=0.07)	+6.1 (p<0.001)	+3.4 (p=0.03)
	Relative	-3.5 (p=0.13)	+9.7 (p<0.001)	+5.3 (p=0.02)
	Versus Placebo			
	Absolute	-2.0 (p=0.36)	+8.6 (p <0.001)	+6.7 (p=0.002)
	Relative	-3.9 (p=0.21)	+12.8 (p<0.001)	+9.2 (p=0.004)

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.

5

Table of Contents

- Cohort 3 - Cohort 3 was designed to evaluate the safety and pharmacokinetics of the 400mg (q12h) dose of VX-809 to support inclusion of this dose in the Phase 3 development program. We evaluated the 400mg (q12h) dose of VX-809 in combination with ivacaftor in Cohort 3 in 11 patients with CF who are homozygous for the F508del mutation. Cohort 3 also included the randomization of four patients to placebo to allow for a blinded safety assessment. Three patients completed treatment in the placebo group. A pharmacokinetic model suggested that 400mg dosing every 12 hours (q12h) of VX-809 would provide a higher total exposure area under the curve, or AUC, compared to 600mg once-daily (QD) dosing, and data from Cohort 3 were consistent with this model.

Safety results from the 400mg (q12h) dose group were similar to that of the 600mg (QD) dose group. In both dose groups, VX-809 was generally well-tolerated alone and in combination with ivacaftor. The most common adverse events in both groups were respiratory in nature. In Cohort 3, one patient in the treatment group discontinued treatment because of a pulmonary adverse event.

Together, these pharmacokinetic and safety data support inclusion of VX-809 400mg (q12h) in combination with ivacaftor 250mg (q12h) in the Phase 3 program to evaluate the effect of higher exposures of VX-809 on efficacy and safety.

The pattern of lung function response observed in Cohort 3 was similar to that observed in the 600mg (QD) dose group in Cohort 2, with a decline in FEV_1 during the VX-809 monotherapy dosing period followed by a statistically significant increase in FEV_1 during the VX-809 and ivacaftor combination dosing period. The within-group mean absolute improvement in FEV_1 observed during the combination-dosing period in Cohort 3 was 6.6 percentage points, compared to 6.1 percentage points for the 600mg (QD) dose group in Cohort 2. Additional lung function results for Cohort 3 are provided below:

		Mean Absolute and Relative Changes in Percent Predicted FEV_1		
		Day 0 - 28; VX-809 Alone	Day 28 - 56; VX-809 + ivacaftor	Day 0 - 56
VX-809 (400mg q12h) + ivacaftor (250mg q12h)	Within Group			
	Absolute	-4.3 (p=0.04)	+6.6 (p=0.01)	+1.9 (p=0.57)
	Relative	-6.3 (p=0.08)	+8.8 (p=0.01)	+2.5 (p=0.67)

In addition to the clinical trials in patients with CF who are homozygous for the F508del mutation, we plan to conduct an 8-week exploratory Phase 2 clinical trial of VX-809 in combination with ivacaftor in patients with CF who are 12 years of age and older and who are heterozygous with a copy of the F508del mutation on one allele and a copy of a second mutation on the other allele that is not expected to respond to either ivacaftor or VX-809 alone. This clinical trial is designed to provide additional safety and lung function data on the combination in heterozygous patients and will evaluate the combination of VX-809 (400mg (q12h)) and ivacaftor (250mg (q12h)).

VX-661

We also are conducting a Phase 2 clinical trial of VX-661, a second CFTR corrector compound. In this clinical trial, we are evaluating VX-661 as both a monotherapy and in combination with ivacaftor in patients with CF who are homozygous for the F508del mutation. The first part of this clinical trial enrolled approximately 120 patients, and we expect to receive data from this clinical trial in the first half of 2013.

HCV INFECTION

Background

The Centers for Disease Control and Prevention, or CDC, have estimated that approximately 2.7 million to 3.9 million people in the United States are chronically infected with HCV. The World Health Organization, or WHO, has estimated that about 170 million people are chronically infected with HCV worldwide. Although exposure to HCV often leads to chronic infection, patients frequently do not have symptoms and are unaware that they have become infected with HCV. Over time, many patients develop liver inflammation. This inflammation can progress to scarring of the liver, called fibrosis, or more advanced scarring of the liver, called cirrhosis. Patients with cirrhosis may go on to develop liver failure or other

Table of Contents

complications, including liver cancer. WHO estimates that HCV infection is responsible for more than 50% of all liver cancer cases and two-thirds of all liver transplants in the developed world.

Genotype 1 HCV infection is the most prevalent form of HCV infection in the United States and the most difficult to treat. There are many other less prevalent HCV infection genotypes, some of which are easier to treat, and each of which tend to respond differently to treatment. Patients who are successfully treated maintain undetectable HCV RNA levels after treatment has been completed, which is referred to as a sustained viral response, or SVR.

The number and type of treatments for HCV infection has and likely will continue to change rapidly. Prior to 2011, patients with genotype 1 HCV infection were treated with a combination of peg-IFN and RBV for 48 weeks. In May 2011, INCIVEK and another HCV protease inhibitor, Merck's VICTRELIS™ (boceprevir), were approved for administration in combination with peg-IFN and RBV. These treatment regimens incorporating HCV protease inhibitors offer substantially increased sustained viral response rates, and in many cases shorter treatment durations, for patients with genotype 1 HCV infection, compared to peg-IFN and RBV alone.

Since INCIVEK's approval in 2011, many companies, including us, have continued to pursue the development of treatment regimens for HCV infection that could potentially offer improved safety, efficacy and/or tolerability, including shorter duration therapies, therapies that do not require the administration of peg-IFN, and therapies that do not cause side effects seen with the currently approved HCV protease inhibitors. Many companies are investigating combination regimens that incorporate one or more of an HCV protease inhibitor, an HCV nucleotide analogue, an HCV non-nucleotide polymerase inhibitor or an NS5A inhibitor, each of which inhibit HCV viral replication through different mechanisms of action. Clinical trials of these investigational combination regimens are being conducted in a wide variety of patient populations, including treatment-naïve and treatment-failure patients, and across all HCV genotypes, which respond differently to different combinations of molecules employing different mechanisms.

In 2012, several companies advanced clinical development programs and released clinical data for potentially competitive treatment regimens. During this period, decreasing numbers of patients with genotype 1 HCV infection started treatment with available treatment options. We believe these decreases are the result of a combination of factors, including new safety and efficacy data that have been reported by our competitors regarding treatment regimens for HCV infection that may become commercially available over the next several years.

We believe that the next drugs that will become commercially available to treat genotype 1 HCV infection will first be approved as part of a treatment regimen that includes peg-IFN and RBV, and that it is likely that one or more of the drug candidates being developed by our competitors will be approved in late 2013 or 2014. All-oral treatment regimens that do not include peg-IFN also are in late-stage development, and it is possible that one or more of these treatment regimens will be approved as soon as late 2014. If one or more treatment regimens with a safety or efficacy profile better than or similar to our INCIVEK-based treatment regimen is approved, we expect that INCIVEK would lose a significant portion of its share of the genotype 1 HCV infection treatment market.

INCIVEK

INCIVEK (telaprevir) is an orally-administered HCV protease inhibitor that is indicated for the treatment of treatment-naïve and treatment-failure adults with genotype 1 HCV infection. Patients who are prescribed an INCIVEK-based treatment regimen receive INCIVEK, peg-IFN, a drug that is administered by weekly injection, and RBV for 12 weeks. After the first 12 weeks, patients stop receiving INCIVEK and continue treatment with peg-IFN and RBV alone for an additional 12 weeks or 36 weeks of treatment. INCIVEK is indicated for three-times-daily dosing, and we recently submitted a supplemental New Drug Application, or sNDA, to the FDA and a supplemental New Drug Submission, or sNDS, to Health Canada for twice-daily dosing. We are conducting Phase 3b clinical trials to evaluate telaprevir-based combination treatment regimens for patients with genotype 1 HCV infection who also have HIV infection and for patients who experience recurrent genotype 1 HCV infection following a liver transplant. Telaprevir was discovered in our collaboration, now ended, with Eli Lilly and Company, and we pay Eli Lilly and Company royalties on net sales of telaprevir.

Table of Contents

HCV Drug Development Programs

Our goal is to improve treatment options available to patients with HCV infection by developing all-oral, interferon-free treatment regimens for HCV infection. The following table summarizes the treatment regimens for HCV infection that we are planning to evaluate:

Drug Candidate	Mechanism(s)
VX-135 (ALS-2200)	
VX-135 in combination with RBV	HCV Nucleotide Analogue/RBV
VX-135 in combination with TMC435	HCV Nucleotide Analogue/HCV Protease Inhibitor
VX-135 in combination with GSK2336805	HCV Nucleotide Analogue/HCV NS5A Inhibitor
VX-135 in combination with VX-222	HCV Nucleotide Analogue/HCV Polymerase Inhibitor
VX-222	
VX-222 in combination with telaprevir and RBV	HCV Polymerase Inhibitor/HCV Protease Inhibitor/RBV

VX-135, an HCV nucleotide analogue, is designed to inhibit the replication of HCV by inhibiting the HCV NS5B polymerase enzyme through mechanisms of action distinct from non-nucleoside HCV polymerase inhibitors such as VX-222. In July 2012, we announced positive results from a Phase 1 clinical trial that evaluated the safety and tolerability of single ascending doses of ALS-2200 (now formulated as VX-135) in healthy volunteers and the safety, tolerability and effects on viral kinetics of multiple ascending doses of ALS-2200 in treatment-naïve patients with genotype 1 HCV infection. In this clinical trial, patients with HCV infection who were dosed with ALS-2200 experienced a dose-dependent, consistent and rapid decline in plasma HCV RNA levels. In the treatment group in which patients received seven days of dosing with 200mg of ALS-2200 once daily, there was a median 4.54 $\log_{10}$ reduction in HCV RNA levels at the end of the dosing period. In the treatment group in which patients received seven days of dosing with 200mg of ALS-2200 once daily in combination with RBV, there was a median 4.18 $\log_{10}$ reduction in HCV RNA levels at the end of the dosing period. In this clinical trial, ALS-2200 was well-tolerated. There were no serious adverse events observed in patients dosed with ALS-2200 and no patients discontinued treatment due to adverse events.

VX-222, a non-nucleoside HCV polymerase inhibitor, is designed to inhibit the replication of HCV by inhibiting the HCV NS5B polymerase. VX-222 has been evaluated in a Phase 2 clinical trial in combination with telaprevir and RBV in treatment-naïve patients with genotype 1 HCV infection.

We are planning to evaluate multiple all-oral treatment regimens for patients with genotype 1 HCV infection in order to determine which regimen or regimens appear likely to provide benefits to patients and to take forward into Phase 3 clinical development. The clinical trials are:

- We are conducting Phase 2 clinical trials to evaluate VX-135 in combination with RBV.
- In October 2012, we entered into a non-exclusive collaboration with Janssen to conduct a clinical trial to evaluate all-oral combinations of Janssen's investigational once-daily HCV protease inhibitor TMC435 (simeprevir), and VX-135. Janssen recently announced positive results from a Phase 3 clinical trial that evaluated TMC435 in combination with peg-IFN and RBV. We expect that Janssen will conduct a drug-drug interaction trial with VX-135 and TMC435 to support the planned initiation of a Phase 2 clinical trial in mid-2013, pending discussions with regulatory authorities. We and Janssen will share equally development costs associated with this collaboration. No further clinical development activities are covered by this agreement beyond the planned Phase 2 clinical trials.
- In October 2012, we entered into a non-exclusive collaboration with GlaxoSmithKline plc to evaluate all-oral combinations of GlaxoSmithKline's investigational once-daily NS5A inhibitor GSK2336805 and VX-135. We expect to initiate the Phase 2 clinical trial to evaluate VX-135 and GSK2336805 in the first half of 2013, pending discussions with regulatory authorities. We and GSK will share equally development costs associated with this collaboration. No further clinical development activities are covered by this agreement beyond the planned Phase 2 clinical trial.
- We are planning to conduct a Phase 2 clinical trial to evaluate VX-135 in combination with our HCV polymerase inhibitor VX-222.

8

Table of Contents

- We are conducting a Phase 2 clinical trial that enrolled approximately 60 patients with genotype 1a HCV infection to evaluate a treatment regimen of telaprevir, VX-222 and RBV.

AUTOIMMUNE DISEASES (RHEUMATOID ARTHRITIS)

Background

Autoimmune diseases, including rheumatoid arthritis, are characterized by inflammation that is believed to be the result of an incorrectly regulated immune response. Rheumatoid arthritis is a chronic disease that affects 0.5% to 1.0% of the world's population and, according to the CDC, approximately 1.5 million adults in the United States. Rheumatoid arthritis causes destruction of joint cartilage and erosion of adjacent bone, resulting in deformity, loss of function and substantial disability. Many patients with rheumatoid arthritis also eventually require joint replacements. While approved drugs, including oral and injectable disease-modifying antirheumatic drugs, or DMARDs, are effective in a portion of patients with rheumatoid arthritis, a significant portion of patients do not respond adequately to DMARDs or experience a decrease in the effectiveness of DMARDs over time. We are seeking to develop an oral therapy for the treatment of rheumatoid arthritis that could be used alone or in combination with existing DMARDs.

VX-509

VX-509 is an investigational oral drug candidate intended to inhibit Janus kinase 3, or JAK3, which is involved in the modulation of a type of white blood cell, referred to as a lymphocyte, that is central to autoimmune disease pathology. Because of JAK3's role in lymphocyte biology, we believe it is a promising target for the design of immunosuppressant drugs for treatment of a variety of autoimmune diseases, including rheumatoid arthritis. Based on in vitro and in vivo data, VX-509 shows promise as a potent and selective inhibitor of JAK3. In 2011, we completed a Phase 2a clinical trial that evaluated VX-509 monotherapy in patients with rheumatoid arthritis. We achieved the two primary endpoints in this Phase 2a clinical trial, defined as a statistically significant improvement in the proportion of patients who achieved at least a 20% improvement in the signs and symptoms of rheumatoid arthritis, also known as ACR20, and a statistically significant improvement from baseline in Disease Activity Score 28, or DAS28.

The most frequently reported class of adverse event in the VX-509 and placebo arms of this Phase 2a clinical trial was infection. The most common individual adverse events observed in this Phase 2a clinical trial, each of which occurred in approximately 5% or less of patients, were nausea, headache and increased alanine transaminase, regardless of treatment arm. Five percent of patients discontinued treatment due to adverse events in the placebo group, compared to eight percent of patients in the VX-509 treatment arms.

Based on the efficacy and safety data from the Phase 2a clinical trial, we initiated a Phase 2b clinical trial in mid-2012 to evaluate once-daily and twice-daily doses of VX-509 in combination with methotrexate. We expect to enroll approximately 350 patients with active moderate-to-severe rheumatoid arthritis and to obtain data from this clinical trial in the second half of 2013. We also recently initiated a Phase 2 clinical trial that is expected to enroll approximately 40 patients with rheumatoid arthritis to evaluate the potential for VX-509 to improve structural joint changes as measured by magnetic resonance imaging and markers of inflammation and joint damage measured in joint fluid.

INFLUENZA

Background: Effects and Prevalence of Influenza

The CDC has estimated that in the United States more than 200,000 patients with influenza infection are hospitalized annually with respiratory and cardiac-related complications. While the number of influenza-related deaths varies significantly depending on the severity of the influenza season, the CDC has estimated the number of influenza-related deaths in the United States averages approximately 25,000 per year. In addition to vaccinations designed to prevent the spread of infection, we believe that there is a significant market for antiviral agents that could potentially be used to treat influenza. Currently, neuraminidase inhibitors, oseltamivir (Tamiflu) and zanamivir (Relenza) are the antiviral agents that are used to treat influenza infection, but these drugs must be administered within 24 to 48 hours of initial infection in order to be effective and do not produce responses in a significant portion of patients.

Table of Contents

VX-787

VX-787 is an investigational drug candidate intended for the treatment of influenza A, which is typically the predominate strain of influenza and includes H1 (pandemic) and H5 (avian) influenza strains. VX-787 aims to treat influenza A through a mechanism that is different from neuraminidase inhibitors. In prioritizing our future development investment, we determined that we would only continue to advance the development of VX-787 as part of a collaboration or if we obtain external funding for this program. We have received final data from a Phase 2 clinical trial of VX-787 that enrolled approximately 140 healthy volunteers who were infected with live influenza virus. We plan to announce the results from this clinical trial in March 2013.

COMMERCIAL ORGANIZATION

Our North American commercial organization supports sales of INCIVEK and KALYDECO in the United States and Canada, and we have established a small international commercial organization to support sales of KALYDECO in other markets. Our sales force and managed markets organizations are responsible for promoting our products to health care providers and payors.

Our U.S. sales force includes approximately 150 employees, most of whom are focused on marketing INCIVEK and have experience in marketing drugs for the treatment of infectious diseases. Our HCV sales force focuses its efforts on those physicians in private practice and at major medical centers who write the majority of prescriptions for HCV therapies, as well as the health care professionals who support their practices. We also have a small sales force dedicated to marketing INCIVEK in Canada.

Our U.S. field-based CF commercial team includes approximately 15 therapeutic specialists who each have experience with CF. We focus our CF marketing efforts in the United States on a relatively small number of physicians and health care professionals who write most of the prescriptions for CF medicines. Many of these physicians and health care professionals are located at one of the approximately 110 accredited centers in the United States focused on the treatment of CF.

We market our products and educate physicians by calling on individual physicians, advertising, sending direct mail, public relations efforts 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.

RESEARCH

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 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 INCIVEK and KALYDECO.

Currently, the therapeutic areas of highest priority to us from a research perspective are: CF and other genetic diseases; infectious diseases; autoimmune diseases; cancer; and neurological diseases and disorders. We plan to focus our research activities on products that would be prescribed by specialist physicians for the treatment of rare or life-threatening diseases that typically affect relatively small patient populations, 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.

Within each therapeutic area, we focus initially on specific medical or disease indications. Driven by the complexity of the therapeutic 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. The objective of this approach is to enable us eventually to provide multiple drugs in each of these therapeutic areas. We select therapeutic areas by mapping our research strengths, including expertise in kinases, proteases and membrane proteins, onto therapeutic areas with high unmet medical need, with an emphasis on indications where based on

scientific insights we believe that we,

Table of Contents

independently or in collaboration with other third parties, will be able to discover, develop and commercialize important medicines for serious diseases.

Our past 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. We are engaged in nonclinical activities involving a number of investigational compounds, one or more of which may enter clinical development in 2013.

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.

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. 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.

Janssen Pharmaceutica, N.V.

In June 2006, we entered into a license, development, manufacturing and commercialization agreement with Janssen. Under the agreement, we collaborate with Janssen on the development and commercialization of telaprevir. We have exclusive commercial rights to telaprevir in North America and lead the development program for INCIVEK (telaprevir) in North America and the Janssen territories. Janssen has exclusive rights to commercialize INCIVO (telaprevir) outside of North America and the Far East.

Janssen pays us a tiered royalty, averaging in the mid-20% range, subject to adjustment for generic competition, if any, as a percentage of net sales of INCIVO in the Janssen territories. Janssen is responsible for certain third-party royalties in its territories. Pursuant to the collaboration agreement, we received an up-front payment of $165.0 million and milestone payments of $350.0 million related to the development and commercialization of INCIVO. We do not expect to receive any further milestone payments pursuant to this agreement. Janssen was responsible for 50% of drug development costs under the development program for North America and the Janssen territories through approval, and continues to be responsible for 50% of drug development costs related to certain post-approval activities. Janssen is required to use diligent efforts to maximize net sales of telaprevir in its territories through its commercial marketing, pricing and contracting strategies. Each of the parties to the collaboration agreement is responsible for drug supply in their respective territories.

Janssen may terminate the agreement upon the later of (i) one year’s advance notice and (ii) such period as may be required to assign and transfer to us specified filings and approvals. The agreement also may be terminated by either party for a material breach by the other, subject to notice and cure provisions. Unless earlier terminated, the agreement will continue in effect until the expiration of Janssen’s royalty obligations, which expire on a country-by-country basis on the later of (a) the last-to-expire patent covering INCIVO or (b) ten years after the first commercial sale in the country. In the European Union, we have a patent covering the composition-of-matter of INCIVO that expires in 2026.

Mitsubishi Tanabe Pharma Corporation

We have a collaboration agreement with Mitsubishi Tanabe pursuant to which Mitsubishi Tanabe has a fully-paid license to manufacture and commercialize TELAVIC (telaprevir) to treat HCV infection in Japan and other specified countries in the Far East. This agreement was entered into in 2004 and amended in 2009. Pursuant to this agreement, Mitsubishi Tanabe provided financial and other support for the development and commercialization of telaprevir, made a $105.0 million

11

Table of Contents

payment to us in connection with the 2009 amendment of the collaboration agreement and made a $65.0 million payment to us in the fourth quarter of 2011 related to the commercialization of TELAVIC in Japan. There are no further payments due to us under this collaboration agreement. Mitsubishi Tanabe is responsible for its own development and manufacturing costs in its territory. Mitsubishi Tanabe may terminate the agreement at any time without cause upon 60 days' prior written notice to us. The agreement also may be terminated by either party for a material breach by the other, subject to notice and cure provisions. Unless earlier terminated, the agreement will continue in effect until the expiration of the last-to-expire patent covering TELAVIC. In Japan, we have a patent covering the composition-of-matter of TELAVIC that expires in 2021.

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, VX-809 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, VX-809, VX-661 and any other compounds discovered during the course of the research collaboration with CFFT and 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 VX-809 and VX-661 and any other compounds discovered during the original research term or the research term that began in 2011. In 2012, we made a commercial milestone payment upon achievement of certain sales levels of KALYDECO and expect that in 2013 we will make the second and final commercial milestone payment that we are obligated to make to CFFT upon the 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 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. CFFT may terminate its funding obligations under the collaboration, as amended, in certain circumstances, in which case there will be a proportional reduction in the royalty rates and commercial milestone payments for certain CFTR corrector compounds. The collaboration also may be terminated by either party for a material breach by the other, subject to notice and cure provisions.

Alios BioPharma, Inc.

In June 2011, we entered into a license and collaboration agreement with Alios BioPharma, Inc., or Alios, a privately-held biotechnology company. Pursuant to the agreement, we are collaborating on the research, development and commercialization of VX-135 (ALS-2200), an HCV nucleotide analogue discovered by Alios. In 2012, we ended development of ALS-2158, a second HCV nucleotide analogue discovered by Alios and licensed to us pursuant to the agreement. We are responsible for all costs related to development and commercialization of VX-135 and are providing funding to Alios for a research program directed to the discovery of additional HCV nucleotide analogues that act on the HCV polymerase.

Under the terms of the agreement, we have exclusive worldwide development and commercialization rights to VX-135 and have the option to select additional compounds discovered in the research program. Upon entering into the agreement, we paid Alios a $60.0 million up-front payment. As of December 31, 2012, Alios had earned an aggregate of $60.0 million in development milestone payments pursuant to the agreement, including a $25.0 million milestone payment in 2012. The agreement provides for development milestone payments to Alios of up to an additional $312.5 million if VX-135 is approved and commercialized. The agreement provides for additional development milestone payments to Alios if a second HCV nucleotide analogue is approved and commercialized. Alios also is eligible to receive commercial milestone payments of up to $750.0 million, as well as tiered royalties on net sales of approved drugs.

We may terminate our agreement with Alios (i) upon 30 days' notice to Alios if we cease development of VX-135 after it has experienced a technical failure and/or (ii) upon 60 days' notice to Alios at any time after we complete

specified Phase 2a clinical trials. The agreement also may be terminated by either party for a material breach by the other, and by Alios for our inactivity or if we challenge certain Alios patents, in each case subject to notice and cure provisions. Unless earlier terminated, the agreement will continue in effect until the expiration of our royalty obligations, which expire on a country-by-

Table of Contents

country basis on the later of (a) the date the last-to-expire patent covering a licensed product expires or (b) ten years after the first commercial sale in the country. In the United States and European Union, there are patent applications pending covering the composition-of-matter of VX-135 that, if granted, would expire in 2031.

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 the 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)
INCIVEK/INCIVO (telaprevir)	Granted (2025)	Granted (2026)
KALYDECO (ivacaftor)	Granted (2027)	Application Pending (2025)
VX-135	Application Pending (2031)	Application Pending (2031)
VX-222	Granted (2030)	Application Pending (2027)
VX-809	Application Pending (2026)	Application Pending (2026)
VX-661	Granted (2027)	Application Pending (2027)
VX-509	Granted (2026)	Application Pending (2025)
VX-787	Application Pending (2030)	Application Pending (2030)

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 patents and patent applications covering telaprevir, VX-222 and other HCV protease and polymerase inhibitors and the use of these compounds to treat HCV infection.
- U.S. and foreign patent applications licensed from Alios covering VX-135 and other HCV nucleotide inhibitors and the use of these compounds to treat HCV infection.
- U.S. and foreign patent applications covering potentiator compounds and corrector compounds for the CFTR protein, including ivacaftor, VX-809 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 inhibitors of a variety of kinase proteins, including VX-509, and the use of those inhibitors to treat autoimmune disease, including rheumatoid arthritis.
- U.S. and foreign patents and patent applications covering influenza virus inhibitors, including VX-787.
- U.S. and foreign patent applications covering the manufacture, pharmaceutical compositions, related solid forms, formulations, dosing regimens and methods of use of these compounds, including our two marketed products telaprevir and ivacaftor.

Table of Contents

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 are entitled to orphan drug exclusivity for ivacaftor in the United States, which means that the FDA may not approve other applications to market ivacaftor for the same indication for seven years except in very limited circumstances. As a result of the seven-year orphan drug marketing exclusivity period, even if a competitor successfully challenges the ivacaftor patent it could not obtain approval from the FDA to market ivacaftor in the United States for at least seven years from the date of approval of ivacaftor in January 2012.

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, including sole source suppliers of certain components of our products and drug candidates, 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. We expect that we will continue for the foreseeable future to rely on third parties to meet most of our commercial and clinical supply needs.

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 contract manufacturers in the European Union and the United States 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. A failure by any of our third-party manufacturers to pass an inspection could adversely affect our ability to distribute INCIVEK (telaprevir) or KALYDECO (ivacaftor) in a timely manner.

Manufacture of INCIVEK (telaprevir)

We require a supply of INCIVEK (telaprevir) for our commercial sales in North America and our clinical trials. We provide a secondary commercial supply source for Janssen through our third-party manufacturers. We believe our efforts to establish and maintain relationships with third-party manufacturers and oversee their activities are important to support consistent supply of INCIVEK.

Janssen manufactures INCIVO (telaprevir) for sale in Janssen's territories and serves as a secondary supply source of drug substance and drug product intermediate for us. We believe there are multiple third parties capable of providing most of the materials and services we need in order to manufacture and distribute INCIVEK. We have limited flexibility to adjust our supply in response to changes in demand, due to the significant lead times required to manufacture INCIVEK. Due in part to this limited flexibility and the INCIVEK inventories we manufactured in previous periods to ensure adequate supply, we recorded significant charges for excess and obsolete INCIVEK inventories in 2012. We currently believe that we have sufficient supply to meet forecasted demand for INCIVEK. In addition, we have significant quantities of materials that we do not expect to utilize.

14

Table of Contents

Manufacture of KALYDECO (ivacaftor)

We require a supply of ivacaftor for commercial sale (as KALYDECO) and for use in our clinical trials. We obtain ivacaftor to meet our commercial and clinical supply needs through a third-party manufacturing network. Our supply chain includes sole source suppliers. A disruption in the commercial supply of KALYDECO for patients would have a significant impact on patients, our business and our product revenues. A disruption in the clinical supply of ivacaftor could delay the completion of clinical trials and impact timelines for filing an sNDA or NDA. Accordingly, we are in the process of establishing secondary sources for our KALYDECO supply needs to reduce the risk of a supply disruption. In 2013, we plan to obtain an alternative source for the active ingredient of ivacaftor, which is a sole-sourced material that is critical to the supply of ivacaftor, and to obtain second source suppliers in 2014 for other components of the ivacaftor supply chain.

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. 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.

HCV Infection

The number and type of treatments for HCV infection has and likely will continue to change rapidly. Factors that may affect the market for any specific HCV treatment regimen, including INCIVEK triple-combination therapy, include the introduction of new competitive drugs or drug combinations, increased sales from currently approved drugs, adverse information regarding the safety characteristics or efficacy of the regimen, significant new information regarding potential treatment regimens being evaluated in clinical trials and enrollment by patients in clinical trials being conducted by us or our competitors.

We market INCIVEK in direct competition with Merck & Co., Inc.'s VICTRELIS (boceprevir), another HCV protease inhibitor that was approved for sale in the United States and Europe in 2011. Patients who are prescribed an INCIVEK-based treatment regimen receive INCIVEK, peg-IFN, a drug that is administered by weekly injection, and RBV for 12 weeks. After the first 12 weeks, patients stop receiving INCIVEK and continue treatment with peg-IFN and RBV alone for an additional 12 weeks or 36 weeks of treatment. In December 2012, we updated the INCIVEK label in the United States to include a Boxed Warning stating that fatal and non-fatal serious skin reactions have been reported in patients taking INCIVEK combination treatment. VICTRELIS is prescribed in a combination regimen with peg-IFN and RBV.

Since INCIVEK's approval in 2011, many companies, including us, have continued to pursue development programs involving HCV drugs and drug candidates with the goal of developing improved treatment regimens for HCV infection. In 2012, several companies advanced clinical development programs and released clinical data for potentially competitive treatment regimens. During this period, decreasing numbers of patients with genotype 1 HCV infection started treatment with available treatment options. We believe these decreases are the result of a combination of factors, including new safety and efficacy data that have been reported by our competitors regarding treatment regimens for HCV infection that may become commercially available over the next several years.

On the basis of clinical data reported by our competitors from numerous late-stage clinical trials, it appears likely that future improvements in HCV treatment regimens will come stepwise, with the next group of drugs to be approved for administration in combination with peg-IFN and RBV, followed quickly by drugs to be co-administered in all-oral

regimens that do not require peg-IFN, an injectable. Gilead Sciences, Inc., or Gilead, and Janssen recently have completed Phase 3 clinical trials evaluating treatment regimens for patients with HCV infection. Gilead announced in February 2013 that it is on-track to make regulatory filings in the second quarter of 2013 for the approval of GS-7977, an HCV nucleotide analogue, in combination with peg-IFN and RBV for treatment-naïve patients with genotype 1, 4, 5 and 6 HCV infection and as part of an all-oral therapy with RBV for the treatment of patients with genotype 2 and 3 HCV infection. Janssen recently completed

Table of Contents

Phase 3 clinical trials evaluating TMC435 in combination with peg-IFN and RBV in patients with genotype 1 HCV infection. The top-line results reported by Gilead and Janssen from these Phase 3 clinical trials suggest that the safety and efficacy profiles of GS-7977 and TMC435 will position them, if approved, to potentially take a significant portion of the market for HCV therapies.

In addition to the HCV treatment regimens that are being developed in combination with peg-IFN and RBV, many companies, including us, are seeking to develop all-oral treatment regimens for HCV infection that could render uncompetitive current and future treatment regimens that include the administration of peg-IFN by injection. We are planning to evaluate potential all-oral treatment regimens that include our HCV nucleotide analogue, VX-135, in Phase 2 clinical trials. Some of our competitors' potential all-oral treatment regimens are more advanced, including all-oral treatment regimens that are being evaluated in Phase 3 clinical trials being conducted by Gilead and Abbvie, Inc. While the development and regulatory timelines for these drug candidates are subject to risk and uncertainty, we believe that (i) substantial additional clinical data regarding potential all-oral treatment regimens will become available in 2013 and (ii) it is possible that one or more all-oral treatment regimens for genotype 1 HCV infection could be commercially available as soon as late 2014. As a result, if we are successful in developing all-oral treatment regimens that include VX-135 and/or VX-222, independently or with a collaborator, it is likely that our all-oral treatment regimens would compete directly with one or more previously approved all-oral treatment regimens.

The following table provides information regarding selected drug candidates that are being evaluated for the treatment of HCV infection.

Drug Candidate	Mechanism	Development Phase
Gilead		
sofosbuvir (GS-7977)	HCV Nucleotide Analogue	Phase 3
GS-9451	HCV Protease Inhibitor	Phase 2
tegobuvir (GS-9190)	Non-nucleoside HCV Polymerase Inhibitor	Phase 2
GS-5885	HCV NS5A Inhibitor	Phase 2
Janssen/Medivir AB		
simeprevir (TMC435)	HCV Protease Inhibitor	Phase 3
TMC647055	Non-nucleoside HCV Polymerase Inhibitor	Phase 2
Abbvie		
ABT-450	HCV Protease Inhibitor	Phase 3
ABT-333	Non-nucleoside HCV Polymerase Inhibitor	Phase 3
ABT-267	HCV NS5A Inhibitor	Phase 3
Vertex		
VX-135	HCV Nucleotide Analogue	Phase 2
VX-222	Non-nucleoside HCV Polymerase Inhibitor	Phase 2
Boehringer Ingelheim		
faldaprevir (BI 201335)	HCV Protease Inhibitor	Phase 3
BI 207127	Non-nucleoside HCV Polymerase Inhibitor	Phase 3
Merck		
vaniprevir (MK-7009)	HCV Protease Inhibitor	Phase 2
Bristol-Myers Squibb		
daclatasvir	HCV NS5A Inhibitor	Phase 3
BMS-650032	HCV Protease Inhibitor	Phase 2
Achillion		
Sovaprevir	HCV Protease Inhibitor	Phase 2
ACH-3102	HCV NS5A Inhibitor	Phase 2
Roche		
danoprevir / RG7227	HCV Protease Inhibitor	Phase 2
setrobuvir	Non-nucleoside HCV Polymerase Inhibitor	Phase 2
GlaxoSmithKline		

GSK2336805	HCV NS5A Inhibitor	Phase 2
Idenix		
IDX719	HCV NS5A Inhibitor	Phase 2

Table of Contents

Where companies have control of multiple drug candidates that span different mechanisms of action, they typically are investigating combination regimens of those drug candidates, with or without the addition of RBV. In addition, many companies, including us, are pursuing a strategy of evaluating drug candidates they control in combination with drug candidates controlled by third parties. For example, we entered into separate non-exclusive collaborations to evaluate VX-135 in combination with Janssen's HCV protease inhibitor TMC435 and GSK's HCV NS5A inhibitor GSK2336805, and Janssen is evaluating TMC435 in combination with Gilead's HCV nucleotide analogue GS-7977 and plans to evaluate TMC435 in combination with Idenix's HCV NS5A Inhibitor IDX719.

Cystic Fibrosis

A number of companies are seeking to identify and develop drug candidates for the treatment of CF, including Novartis, Pfizer, Genzyme and several private companies. We believe our competitors have research and development programs directed at identifying CFTR potentiators, CFTR correctors and drug candidates with other mechanisms of action with the goal of addressing the underlying cause of CF. While we believe that it will be several years before any of these competitive programs enter late-stage clinical development, if one or more competing therapies are successfully developed as a treatment for patients with CF, our revenues from KALYDECO and/or our other CF drug candidates, if then approved, could face competitive pressures.

GOVERNMENT REGULATION

The research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, 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 pending applications;
- withdrawal of an approval;
- imposition of a clinical hold;
- warning 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;

Table of Contents

- 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:

Table of Contents

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.

Concurrently with clinical trials, companies usually complete additional 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

Table of Contents

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.

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

20

Table of Contents

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 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

Table of Contents

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 VX-809 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 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 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 assure 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.

Breakthrough Therapy Designation

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 new 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. At this time, because this designation was provided pursuant to a newly enacted law and our programs were the first to receive this designation, we cannot determine if there will be any specific implications of the Breakthrough Therapy designations on our development programs.

Reimbursement

Sales of our products depend, in part, 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.

22

Table of Contents

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 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. In 2012 and 2011, our rebates associated with the Medicare Part D "donut hole" were $1.8 million and $1.4 million, respectively. In 2012 and 2011, we recorded $1.8 million and $0, respectively, in sales, general and administrative expenses related to the branded prescription drug fee established pursuant to the ACA. 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 any other drug candidates we may develop, depends largely on obtaining and maintaining government reimbursement, because in many foreign countries patients are unlikely to use 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 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.

Table of Contents

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 new 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,

Table of Contents

regulations were released that contain detailed guidance regarding the information that must be collected and reported. We will be required to collect information regarding such payments starting in August 2013 and to begin reporting such information in March 2014. Over the next several years, we will need 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.

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.

EMPLOYEES

As of December 31, 2012, we had approximately 2,200 employees. The number of our employees increased by approximately 10% during 2012, from approximately 2,000 on December 31, 2011. We are likely to further increase our headcount in 2013. Of these employees, approximately 1,950 were based in the United States, 175 were based in Europe and 75 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 both 2011 and 2012. 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 W, "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 is 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 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, 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 130 Waverly Street, Cambridge, Massachusetts 02139. We have research sites located in San Diego, California; Coralville, Iowa; Montreal, Canada and Milton Park, U.K. We also have an office in Washington, D.C. We have established our European headquarters in Switzerland and have offices in France, Germany, Ireland and the United Kingdom.

Table of Contents

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.	57	Chairman of the Board, President and Chief Executive Officer
Stuart A. Arbuckle	47	Executive Vice President and Chief Commercial Officer
Kenneth L. Horton	46	Executive Vice President and Chief Legal Officer
Peter Mueller, Ph.D.	56	Executive Vice President, Global Research and Development, and Chief Scientific Officer
Ian F. Smith	47	Executive Vice President and Chief Financial Officer
Megan Pace	40	Senior Vice President, Corporate Communications
Amit K. Sachdev, J.D.	45	Senior Vice President, Global Government Strategy, Market Access and Value
Christiana Stamoulis, M.B.A.	42	Senior Vice President, Corporate Strategy and Business Development
Paul M. Silva	47	Senior Vice President and Corporate Controller
David Altshuler, M.D., Ph.D.	48	Director
Joshua S. Boger, Ph.D.	61	Director
Matthew W. Emmens	61	Director
Terrence C. Kearney	58	Director
Yuchun Lee	47	Director
Margaret G. McGlynn	53	Director
Wayne J. Riley, M.D., M.B.A.	53	Director
Bruce I. Sachs	53	Director
Elaine S. Ullian	65	Director

Dr. Leiden is our Chairman, Chief Executive Officer and President. He has held the positions of Chief Executive Officer and President since February 2012 after joining us as CEO Designee in December 2011. He has been a member of our Board of Directors since July 2009, the Chairman of our Board of Directors since May 2012, and served as our lead independent director from October 2010 through December 2011. Dr. Leiden was a Managing Director at Clarus Ventures, a life sciences venture capital firm, from 2006 through January 2012. Dr. Leiden was President and Chief Operating Officer of Abbott Laboratories, Pharmaceuticals Products Group, and a member of the Board of Directors of Abbott Laboratories from 2001 to 2006. From 1987 to 2000, Dr. Leiden held several academic appointments, including the Rawson Professor of Medicine and Pathology and Chief of Cardiology and Director of the Cardiovascular Research Institute at the University of Chicago, the Elkan R. Blout Professor of Biological Sciences at the Harvard School of Public Health, and Professor of Medicine at Harvard Medical School. He is an elected member of both the American Academy of Arts and Sciences, and the Institute of Medicine of the National Academy of Sciences. Dr. Leiden is a senior advisor to Clarus Ventures. Dr. Leiden was a director and the non-executive Vice Chairman of the board of Shire plc, a specialty biopharmaceutical company, from 2006 to January 2012, and was also a member of the Board of Directors of Millennium Pharmaceuticals, Inc. from October 2007 until it was acquired in June 2008. Dr. Leiden received his M.D., Ph.D. and B.A. degrees from the University of Chicago.

Mr. Arbuckle is our Executive Vice President and Chief Commercial Officer, a position he has held since September 2012. Prior to joining us, Mr. Arbuckle held multiple commercial leadership roles at Amgen, Inc., a 17,000 person biotechnology company, from July 2004 through August 2012. Mr. Arbuckle has worked in the biopharmaceuticals industry since 1986, including more than 15 years at GlaxoSmithKline plc, where he held sales and marketing roles of increasing responsibility for medicines aimed at treating respiratory, metabolic, musculoskeletal, cardiovascular and other diseases. He currently is a member of the Board of Directors of the Cancer Support Community, an international non-profit dedicated to providing support, education and hope to people affected by cancer. Mr. Arbuckle holds a BSc in pharmacology and physiology from the University of Leeds.

Mr. Horton is our Executive Vice President and Chief Legal Officer, a position he has held since June 2012. Prior to joining us, Mr. Horton served as General Counsel and Executive Vice President of Corporate Development at Nordion

Inc. (formerly MDS Inc.), a global health science company, from 2005 to 2011. He joined MDS from PerkinElmer, Inc., where

Table of Contents

he was Vice President, Acquisitions, Ventures and General Counsel for the Life and Analytical Sciences business unit. Mr. Horton began his legal career practicing corporate law at Ropes & Gray in Boston after working as a strategy consultant in the United States and Europe. Mr. Horton currently serves on the Board of Advisors for Beth Israel Deaconess-Needham Hospital and was formerly Chairman of Lumira Capital. Mr. Horton holds an A.B. from Dartmouth College, a J.D. from Harvard Law School and was awarded the D.A.A.D. Direktstipendium for study at the Universitaet Bonn.

Dr. Mueller is our Executive Vice President, Global Research and Development, a position he has held since May 2009, and has been our Chief Scientific Officer since July 2003. Dr. Mueller was our Executive Vice President, Drug Innovation and Realization, from February 2006 to May 2009, and our Senior Vice President, Drug Discovery and Innovation, from July 2003 to February 2006. Prior to joining us, Dr. Mueller was the Senior Vice President, Research and Development, of Boehringer Ingelheim Pharmaceuticals, Inc., with responsibility for the development of all drug candidates in the company's portfolio in North America. He led research programs in the areas of immunology, inflammatory cardiovascular disease and gene therapy on a global basis. During his time with Boehringer Ingelheim, Dr. Mueller oversaw the discovery of numerous development candidates and held several positions in basic research, medicinal chemistry and management. Dr. Mueller received both an undergraduate degree and a Ph.D. in chemistry at the Albert Einstein University of Ulm, Germany, where he also holds a Professorship in Theoretic Organic Chemistry. He completed fellowships in quantum pharmacology at Oxford University and in biophysics at Rochester University.

Mr. Smith is our Executive Vice President and Chief Financial Officer, a position he has held since February 2006. From November 2003 to February 2006, he was our Senior Vice President and Chief Financial Officer, and from October 2001 to November 2003, he served as our Vice President and Chief Financial Officer. Prior to joining us, Mr. Smith served as a partner in the Life Science and Technology Practice Group of Ernst & Young LLP, an accounting firm, from 1999 to 2001. Mr. Smith initially joined Ernst & Young's U.K. firm in 1987, and then joined its Boston office in 1995. Mr. Smith currently is a member of the Boards of Directors of Acorda Therapeutics, Inc., a drug development company, and Infinity Pharmaceuticals, Inc., a drug development company. Mr. Smith holds a B.A. in accounting and finance from Manchester Metropolitan University, U.K., is a member of the American Institute of Certified Public Accountants and is a Chartered Accountant of England and Wales.

Ms. Pace is our Senior Vice President, Corporate Communications, a position she has held since July 2012. Ms. Pace served as our Vice President, Corporate Communications from May 2010 through July 2012. Prior to joining us, Ms. Pace was a Senior Director at Genentech, Inc., a biotechnology company, from 2005 through April 2010, where she led the team responsible for public affairs, product public relations and patient advocacy. Prior to Genentech, she held government affairs and public relations roles at Eli Lilly & Company, and worked at Porter Novelli, a global public relations firm, where she managed disease awareness and public health campaigns for several biopharmaceutical companies and government agencies. Ms. Pace holds a B.A. from the College of Charleston.

Mr. Sachdev is our Senior Vice President, Global Government Strategy, Market Access and Value, a role he assumed in February 2013. As a Senior Vice President, he has led our government affairs, public policy and patient advocacy functions since he joined us in July 2007 and built and managed our Canadian business operations from October 2010 through February 2013. Mr. Sachdev served as Executive Vice President, Health of the Biotechnology Industry Organization (BIO) from April 2005 through June 2007. Mr. Sachdev was the Deputy Commissioner for Policy at the FDA from April 2004 through April 2005, and held several other senior positions within the FDA from September 2002 through April 2004. From 1998 to 2002, Mr. Sachdev served as Majority Counsel to the Committee on Energy and Commerce in the United States House of Representatives. From 1993 to 1997, Mr. Sachdev practiced law, first at the Chemical Manufacturers Association, and then with the law firm of Ropes & Gray. Mr. Sachdev holds a B.S from Carnegie Mellon University, and a J.D. from Emory University School of Law.

Ms. Stamoulis is our Senior Vice President, Corporate Strategy and Business Development, a position she has held since October 2009. Prior to joining us, she was a Managing Director in Citigroup's Healthcare Banking Group from April 2006 to February 2009. From 2000 to April 2006, Ms. Stamoulis was an investment banker in the Healthcare Investment Banking Group of Goldman, Sachs & Co., where she was a Vice President from January 2002 through April 2006. Ms. Stamoulis started her career as a strategy consultant at The Boston Consulting Group. Ms. Stamoulis is a member of the Board of Directors of Hologic, Inc., a company focused on diagnostics, medical imaging systems

and surgical products for women. Ms. Stamoulis holds a B.S. in Economics and a B.S. in Architecture from the Massachusetts Institute of Technology and an M.B.A. from the MIT Sloan School of Management.

Table of Contents

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

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

Dr. Boger is the founder of Vertex and has been a director since our inception in 1989. He was our Chief Executive Officer from 1992 through May 2009. He was our Chairman of the Board from 1997 until May 2006 and our President from our inception until December 2000, and from 2005 through February 2009. He was our Chief Scientific Officer from 1989 until May 1992. Prior to founding Vertex in 1989, Dr. Boger held the position of Senior Director of Basic Chemistry at Merck Sharp & Dohme Research Laboratories in Rahway, New Jersey, where he headed both the Department of Medicinal Chemistry of Immunology & Inflammation and the Department of Biophysical Chemistry. Dr. Boger holds a B.A. in chemistry and philosophy from Wesleyan University and M.S. and Ph.D. degrees in chemistry from Harvard University.

Mr. Emmens was our Chief Executive Officer from May 2009 through January 2012, our President from February 2009 through January 2012 and our Executive Chairman from February 2012 through May 2012. He has been a member of our Board of Directors since 2004 and was the Chairman of our Board of Directors from May 2009 through May 2012. Mr. Emmens is the Chairman of the Board of Directors of Shire plc, and has been a member of Shire's board since March 2003. From March 2003 to June 2008, Mr. Emmens was also the Chief Executive Officer of Shire plc. Before joining Shire in 2003, Mr. Emmens served as President of Merck KGaA's global prescription pharmaceuticals business in Darmstadt, Germany. In 1999, he joined Merck KGaA and established EMD Pharmaceuticals, Inc., its United States prescription pharmaceutical business. Mr. Emmens held the position of President and Chief Executive Officer at EMD Pharmaceuticals from 1999 to 2001. Prior to this, Mr. Emmens held various positions, including Chief Executive Officer, at Astra Merck, Inc. as well as several positions at Merck & Co., Inc. Mr. Emmens was a member of the Board of Directors of Incyte Corporation, a drug development company, from 2006 through February 2009. Mr. Emmens received a B.S. degree in business management from Farleigh Dickinson University.

Mr. Kearney has been a member of our Board of Directors since May 2011. Mr. Kearney served as the Chief Operating Officer of Hospira, Inc., a specialty pharmaceutical and medication delivery company, from April 2006 to January 2011. From April 2004 to April 2006, he served as Hospira's Senior Vice President, Finance, and Chief Financial Officer, and he served as Acting Chief Financial Officer through August 2006. Mr. Kearney served as Vice President and Treasurer of Abbott Laboratories from 2001 to April 2004. From 1996 to 2001, Mr. Kearney was Divisional Vice President and Controller for Abbott's International Division. He received his B.S. in biology from the University of Illinois and his M.B.A. from the University of Denver.

Mr. Lee has been a member of our Board of Directors since September 2012. Mr. Lee was the Vice President of IBM's Enterprise Marketing Management Group from November 2010 through January 2013. Mr. Lee co-founded Unica Corporation, a provider of software and services used to automate marketing processes, in 1992, and was Unica's President and/or Chief Executive Officer from 1992 through November 2010, when Unica was acquired by

IBM. From 1989 to 1992, Mr. Lee was a senior consultant at Digital Equipment Corporation, a supplier of general computing technology and consulting services. Mr. Lee holds a B.S. and M.S. in electrical engineering and computer science from the Massachusetts Institute of Technology and an M.B.A. from Babson College.

Ms. McGlynn has been a member of our Board of Directors since May 2011. Ms. McGlynn has served as the President and Chief Executive Officer of the International AIDS Vaccine Initiative, a global not-for-profit organization whose mission

Table of Contents

is to ensure the development of safe, effective and accessible HIV vaccines for use throughout the world, since July 2011. Ms. McGlynn served as President, Vaccines and Infectious Diseases of Merck & Co., Inc. from 2005 until 2009. Ms. McGlynn joined Merck in 1983 and served in a variety of marketing, sales and managed care roles. Currently, Ms. McGlynn serves as a member of the Board of Directors for Air Products and Chemicals, Inc., a company specializing in gases and chemicals for industrial uses, and Amicus Therapeutics, Inc., a biopharmaceutical company. She is also a member of the National Industrial Advisory Committee at the University at Buffalo School of Pharmacy and Pharmaceutical Sciences. Ms. McGlynn holds a B.S. in Pharmacy and an M.B.A. in Marketing from the State University of New York at Buffalo.

Dr. Riley has been a member of our Board of Directors since July 2010. Dr. Riley is President and Chief Executive Officer of Meharry Medical College, a position he has held since January 2007. In addition, he holds the academic rank of Professor of Internal Medicine at both Meharry and Vanderbilt University Schools of Medicine. From May 2004 to December 2006, Dr. Riley served as a corporate officer and member of the executive management team as Vice President and Vice Dean for Health Affairs and Governmental Relations and Associate Professor of Medicine at Baylor College of Medicine, and Assistant Chief of Medicine at Ben Taub General Hospital, Baylor's primary adult public hospital teaching affiliate. He served as Assistant Dean for Education at Baylor College of Medicine from 2000 to 2004. Dr. Riley is a member of the Board of Directors of Pinnacle Financial Partners, Inc., a financial services holding firm, and HCA Holdings, Inc., a leading operator of hospitals and health facilities. Dr. Riley earned a B.A. from Yale University, an M.P.H. in health systems management from the Tulane University School of Public Health and Tropical Medicine, an M.D. from the Morehouse School of Medicine and an M.B.A. from the Jones Graduate School of Business, Rice University.

Mr. Sachs has been a member of our Board of Directors since 1998. He is a General Partner at Charles River Ventures, a venture capital firm he joined in 1999. From 1998 to 1999, he served as Executive Vice President and General Manager of Ascend Communications, Inc. From 1997 until 1998, Mr. Sachs served as President and Chief Executive Officer of Stratus Computer, Inc. From 1995 to 1997, he served as Executive Vice President and General Manager of the Internet Telecom Business Group at Bay Networks, Inc. From 1993 to 1995, he served as President and Chief Executive Officer at Xylogics, Inc. Mr. Sachs was a director of BigBand Networks, Inc., a network-based platform company, from 2005 through June 2009. Mr. Sachs holds a B.S.E.E. in electrical engineering from Bucknell University, an M.E.E. in electrical engineering from Cornell University, and an M.B.A. from Northeastern University.

Ms. Ullian has been a member of our Board of Directors since 1997. From 1996 through January 2010, she served as President and Chief Executive Officer of Boston Medical Center, a private, not-for-profit, 626-bed, academic medical center with a community-based focus. From 1994 to 1996, she served as President and Chief Executive Officer of Boston University Medical Center Hospital. From 1987 to 1994, Ms. Ullian served as President and Chief Executive Officer of Faulkner Hospital. She also serves as a director of Thermo Fisher Scientific Inc. and Hologic, Inc. Ms. Ullian holds a B.A. in political science from Tufts University and an M.P.H. from the University of Michigan.

Table of Contents

ITEM 1A. RISK FACTORS

RISK FACTORS

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

Risks Related to Our Products

A majority of our revenues are due to sales of INCIVEK (telaprevir) in the United States, and our future revenues from INCIVEK are expected to decline.

In 2012, 87% of our total net product revenues were attributable to INCIVEK. Our net product revenues from sales of INCIVEK declined over the course of 2012. While we expect INCIVEK net product revenues to decline in 2013 as compared to 2012, we cannot accurately predict the extent of this decline. If our INCIVEK net product revenues, market share and/or other information regarding sales of INCIVEK do not meet the expectations of investors or public market analysts, the market price of our common stock may decline.

The number and type of treatments for HCV infection has and likely will continue to change rapidly. Factors that may affect the market for any specific HCV treatment regimen, including INCIVEK triple-combination therapy, include the introduction of new competitive drugs or drug combinations, increased sales from currently approved drugs, adverse information regarding the safety characteristics or efficacy of the regimen, significant new information regarding potential treatment regimens being evaluated in clinical trials and enrollment by patients in clinical trials being conducted by us or our competitors. We believe the decreases in INCIVEK net product revenues that we experienced in 2012 are the result of a combination of factors, including the safety and efficacy data that have been reported by our competitors regarding treatment regimens for HCV infection that may become commercially available over the next several years.

We market INCIVEK in direct competition with Merck & Co., Inc.'s VICTRELIS (boceprevir), another HCV protease inhibitor that was approved for sale in 2011. Since INCIVEK's approval in 2011, many companies have continued to pursue the development of treatment regimens for HCV infection that could potentially offer improved safety, efficacy and/or tolerability, including shorter duration therapies, therapies that do not require the administration of peg-IFN, and therapies that do not cause side effects seen with the currently approved HCV protease inhibitors. Many companies are investigating combination regimens that incorporate one or more of an HCV protease inhibitor, an HCV nucleotide analogue, an HCV non-nucleotide polymerase inhibitor or an NS5A inhibitor, each of which inhibit HCV viral replication through different mechanisms of action. Clinical trials of these investigational combination regimens are being conducted in a wide variety of patient populations, including treatment-naïve and treatment-failure patients, and across all HCV genotypes, which respond differently to different combinations of molecules employing different mechanisms.

On the basis of clinical data reported by our competitors from numerous late-stage clinical trials, it appears likely that future improvements in HCV treatment regimens will come stepwise, with the next group of drugs to be approved for administration in combination with peg-IFN and RBV, followed quickly by drugs to be co-administered in all-oral regimens that do not require peg-IFN, an injectable. Gilead's GS-7977, an HCV nucleotide analogue, and Janssen's TMC435, an HCV protease inhibitor, have been evaluated in Phase 3 clinical trials. The top-line results reported by Gilead and Janssen from these Phase 3 clinical trials suggest that the safety and efficacy profiles of GS-7977 and TMC435 will position them, if approved, to potentially take a significant portion of the market for HCV therapies. While it is difficult to estimate regulatory timelines and the response of regulatory agencies to submissions for marketing approval, we believe it is likely that GS-7977-based and/or TMC435-based treatment regimens will be approved in one or more markets as a treatment for genotype 1 HCV infection in late 2013 or 2014.

In addition to the HCV treatment regimens that are being developed in combination with peg-IFN and RBV, many all-oral treatment regimens for HCV infection are in development that could render uncompetitive current and future treatment regimens that include the administration of peg-IFN by injection. We are planning to evaluate all-oral treatment regimens that include our HCV nucleotide analogue, VX-135, in Phase 2 clinical trials. Some of our

competitors' potential all-oral treatment regimens are more advanced, including all-oral treatment regimens that are being evaluated in Phase 3 clinical

Table of Contents

trials being conducted by Gilead and Abbvie, Inc. While the development and regulatory timelines for these drug candidates are subject to risk and uncertainty, we believe that (i) substantial additional clinical data regarding potential all-oral treatment regimens will become available in 2013 and (ii) it is possible that one or more all-oral treatment regimens for genotype 1 HCV infection could be commercially available as soon as late 2014. As a result, if we are successful in developing all-oral treatment regimens that include VX-135 and/or VX-222, independently or with a collaborator, it is likely that our all-oral treatment regimens would compete directly with one or more previously approved all-oral treatment regimens.

If one or more treatment regimens with a similar or better efficacy, safety and/or tolerability profile than our telaprevir-based treatment regimen, is approved, we expect that INCIVEK would lose a significant portion of its share of the genotype 1 HCV infection treatment market.

Our future revenues from KALYDECO monotherapy are dependent, among other factors, on the outcomes of reimbursement discussions in international markets and ongoing clinical trials in which we are evaluating ivacaftor in additional patient groups.

In 2012, we obtained approval to market KALYDECO (ivacaftor) in the United States, Canada and the European Union for the treatment of patients with CF six years of age and older with the G551D mutation in the CFTR gene. Since its approval in the first quarter of 2012, most eligible patients in the United States have initiated and are receiving treatment with KALYDECO. We are in discussions regarding reimbursement for KALYDECO in multiple international markets. In France and Germany, we began commercial sales of KALYDECO in 2012, but we are continuing to discuss the reimbursement rate we will receive for KALYDECO in future periods. Funding for KALYDECO has been recommended in England and Ireland, and we anticipate that reimbursement in these countries will begin in the second quarter of 2013. In other countries, we must first complete the reimbursement discussions before we commence commercial sales. There can be no assurance that we will be able to obtain, obtain on a timely basis, or maintain appropriate reimbursement for KALYDECO in these international markets.

In order to expand the market for ivacaftor monotherapy, we will need to demonstrate that ivacaftor is safe and effective in additional patient populations. We are conducting three Phase 3 clinical trials and one Phase 2 clinical trial to evaluate ivacaftor as a monotherapy in additional patient populations, including patients younger than six years of age with gating mutations and patients with other mutations in the CFTR gene. These clinical trials are subject to many of the same risks and uncertainties that are described in these risk factors with respect to the development of our drug candidates. Even if these clinical trials are successful, we do not expect that we would obtain approval for the use of ivacaftor in additional populations until 2014 or later.

We cannot predict the royalty revenues we will receive based on INCIVO sales by Janssen in its territories.

Janssen began marketing INCIVO (telaprevir) in the second half of 2011, and we earned $117.6 million in royalty revenues on net sales of INCIVO by Janssen in 2012. In addition to the factors that contribute to the uncertainty of sales of INCIVEK (telaprevir) by us in the United States, which apply equally to Janssen's sales in its territories, sales in Janssen's territories are dependent upon Janssen's sales and marketing efforts, which we do not control and may not be able to effectively influence, and the actions and decisions of foreign regulatory authorities. We cannot predict the royalty revenues that we will recognize in future periods from sales of INCIVO by Janssen or the timing of such revenues.

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

INCIVEK, KALYDECO and any drugs we develop in the future may not be able to compete effectively with marketed drugs or new drugs that may be developed by competitors. There are many other companies developing drugs for the same indications that we are pursuing. In order to compete successfully in these areas, we must demonstrate improved safety, efficacy and/or tolerability, and ease of manufacturing, and gain and maintain market acceptance over competing drugs. Many of our competitors, including major pharmaceutical companies such as Abbvie, Bristol-Myers Squibb, Gilead, Johnson & Johnson, Merck, Novartis, Pfizer, Sanofi and Roche, possess substantially greater financial, technical and human resources than we possess.

We are aware of a number of companies that are developing new treatments for HCV infection, including HCV nucleotide analogues, HCV protease inhibitors, non-nucleoside HCV polymerase inhibitors and HCV NS5A

inhibitors. Although drug development is a lengthy process and involves a high degree of risk, we expect that over the next several years

Table of Contents

several of these competitive HCV drug candidates may be approved as part of treatment regimens for HCV infection in the United States and elsewhere in the world. As a result, the commercial prospects for INCIVEK, and VX-135 and VX-222, if approved, will depend on, among other factors:

- the efficacy, safety, tolerability and other characteristics of any combination therapy including INCIVEK, VX-135 and/or VX-222 relative to existing and future treatments for HCV infection;
- our ability to establish VX-135 and/or VX-222, if approved, or INCIVEK as a significant component of any commercially competitive all-oral therapy for the treatment of HCV infection; and
- the clinical data obtained and timing of marketing approvals for drug candidates being developed by our competitors, including any all-oral therapy or shorter duration therapy for the treatment of HCV infection.

One or more competing therapies for the treatment of HCV infection may be approved in late 2013 or 2014 with a similar or better efficacy, safety and/or tolerability profile than our telaprevir-based treatment regimen, which would negatively affect INCIVEK and INCIVO sales and could negatively affect our business and financial condition.

A number of companies are seeking to identify and develop drug candidates for the treatment of CF, including Novartis, Pfizer, Genzyme and several private companies. We believe our competitors have research and development programs directed at identifying CFTR potentiators, CFTR correctors and drug candidates with other mechanisms of action with the goal of addressing the underlying cause of CF. While we believe that it will be several years before any of these competitive programs enter late-stage clinical development, if one or more competing therapies are successfully developed as a treatment for patients with CF, our revenues from KALYDECO and/or other compounds, if then approved, could face competitive pressures.

If we discover safety issues with either of our products that were not known at the time of approval or if we fail to comply with continuing U.S. and applicable foreign regulations, commercialization efforts for the product could be negatively affected, the approved product could lose its approval or sales could be suspended, and our business could be materially harmed.

Our products are subject to continuing regulatory oversight, including the review of additional safety information. Drugs are more widely used by patients once approval has been obtained and therefore side-effects and other problems may be observed after approval that were not seen or anticipated, or were not as prevalent or severe, during pre-approval clinical trials or nonclinical studies. For example, in December 2012, we updated the INCIVEK label in the United States to include a Boxed Warning stating that fatal and non-fatal serious skin reactions have been reported in patients taking INCIVEK combination treatment. The subsequent discovery of previously unknown problems with a product could negatively affect commercial sales of the product, result in restrictions on the product or lead to the withdrawal of the product from the market. The reporting of adverse safety events involving our products or public speculation about such events could cause our stock price to decline or experience periods of volatility.

If we or our collaborators fail to comply with applicable continuing regulatory requirements, we or our collaborators may be subject to fines, suspension or withdrawal of regulatory approvals for specific products, product recalls and seizures, operating restrictions and/or criminal prosecutions. In addition, the manufacturers we engage to make our products and the manufacturing facilities in which our products are made are subject to periodic review and inspection by the FDA and foreign regulatory authorities. If problems are identified during the review or inspection of these manufacturers or manufacturing facilities, it could result in our inability to use the facility to make our product or a determination that inventories are not safe for commercial sale.

If physicians, patients and third-party payors do not accept our drugs, we may be unable to generate significant revenues in future periods.

Our drugs may not gain or maintain market acceptance among physicians and patients. Effectively marketing INCIVEK and KALYDECO, and any of our other drug candidates, if approved, requires substantial efforts, both prior to launch and after approval. Physicians may elect not to prescribe our drugs, and patients may elect not to request or take them, for a variety of reasons including:

Table of Contents

- lower demonstrated efficacy, safety and/or tolerability compared to other drugs;
- prevalence and severity of adverse side-effects;
- lack of cost-effectiveness;
- lack of reimbursement availability from third-party payors;
- a decision to wait for the approval of other therapies in development that have significant perceived advantages over our applicable drug;
- convenience and ease of administration;
- other potential advantages of alternative treatment methods; and