VERTEX PHARMACEUTICALS INC / MA
Form 10-K
February 19, 2010

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Table of Contents

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10-K

ý **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the Fiscal Year Ended December 31, 2009

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) 444-6100**

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
Rights to Purchase Series A Junior Participating Preferred Stock	

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

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ý 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 ý

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 ý No o

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes o 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 ý	Accelerated filer o	Non-accelerated filer o (Do not check if a smaller reporting company)	Smaller reporting company o

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

The aggregate market value of the registrant's common stock held by non-affiliates of the registrant (without admitting that any person whose shares are not included in such calculation is an affiliate) based on the last reported sale price of the common stock on June 30, 2009 (the last trading day of the registrant's second fiscal quarter of 2009) was $6.4 billion. As of February 16, 2010, the registrant had 200,576,408 shares of common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the definitive Proxy Statement for the 2010 Annual Meeting of Stockholders to be held on May 13, 2010 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.

"Vertex" is a registered trademark of Vertex. "Lexiva" and "Telzir" are registered trademarks of GlaxoSmithKline plc. Other brands, names and trademarks contained in this Annual Report on Form 10-K are the property of their respective owners.

Table of Contents

PART I

ITEM 1. BUSINESS

OVERVIEW

We are in the business of discovering, developing and commercializing small molecule drugs for the treatment of serious diseases. Telaprevir, our lead drug candidate, is an oral hepatitis C protease inhibitor and one of the most advanced of a new class of antiviral treatments in clinical development that target hepatitis C virus, or HCV, infection. Telaprevir is being evaluated in a registration program focused on treatment-naïve and treatment-failure patients with genotype 1 HCV infection. We currently intend to submit a new drug application, or NDA, for telaprevir in the United States in the second half of 2010 and to initiate sales of telaprevir in the United States in 2011, assuming the successful completion of the registration program.

We are engaged in a number of other clinical development programs and intend to continue to invest in our research programs with the goal of adding promising new compounds to our drug development pipeline. VX-770, the lead drug candidate in our cystic fibrosis, or CF, program is being evaluated in a registration program that focuses on patients with CF who have the G551D mutation in the gene responsible for CF. We are conducting or are planning to begin in 2010 a number of Phase 2a clinical trials of our earlier-stage drug candidates. These clinical trials consist of a planned clinical trial that will evaluate telaprevir in combination with the HCV polymerase inhibitor VX-222, a planned clinical trial of VX-809 in combination with VX-770 in patients with the most common mutation in the gene responsible for CF, a clinical trial of VX-509 in patients with moderate-to-severe rheumatoid arthritis and a clinical trial of VX-765 in patients with treatment-resistant epilepsy.

OUR PIPELINE

Our pipeline is described in the following table. In addition to those listed below, we are engaging in preclinical activities with respect to a number of additional drug candidates.

Drug or Drug Candidate	Clinical Indication(s)	Mechanism/Target	Development Stage	Collaborator(s)
HCV Infection				
telaprevir (VX-950)	HCV Infection	HCV Protease Inhibitor	Phase 3	Janssen Pharmaceutica, N.V. Mitsubishi Tanabe Pharma Corporation
VX-222	HCV Infection	HCV Polymerase Inhibitor	Phase 2a	
VX-985	HCV Infection	HCV Protease Inhibitor	Phase 1	
VX-759	HCV Infection	HCV Polymerase Inhibitor	Phase 1	
Cystic Fibrosis				
VX-770	Cystic Fibrosis	CFTR Potentiator	Phase 3	Cystic Fibrosis Foundation Therapeutics Incorporated
VX-809	Cystic Fibrosis	CFTR Corrector	Phase 2a	Cystic Fibrosis Foundation Therapeutics Incorporated
Immune-mediated Inflammatory Diseases				
VX-509	Rheumatoid Arthritis	JAK3 Inhibitor	Phase 2a	
Epilepsy				
VX-765	Epilepsy	Caspase-1 Inhibitor	Phase 2a	
HIV Infection				
Lexiva/Telzir	HIV Infection	HIV Protease Inhibitor	Marketed	GlaxoSmithKline plc*

* We sold our rights to future royalties from sales of Lexiva/Telzir in May 2008.

Table of Contents

OUR STRATEGY

Our goal is to become a fully-capable biopharmaceutical company with industry-leading capabilities in the research, development and commercialization of innovative drugs that provide substantial benefits to patients with serious diseases. The key elements of our strategy are:

Obtain FDA approval for and effectively commercialize telaprevir in the United States. We are focused on obtaining approval for and effectively commercializing telaprevir as a treatment for patients infected with genotype 1 HCV who have not received previous treatment for their infections, referred to as treatment-naïve patients, and patients infected with genotype 1 HCV who have failed to achieve a sustained viral response, or SVR, after prior treatment with pegylated-interferon, or peg-IFN, and ribavirin, or RBV, referred to as treatment-failure patients. Our registration program is designed to support 24-week response-guided telaprevir-based treatment regimens for treatment-naïve patients, and to support treatment of all categories of treatment-failure patients, including null responders to peg-IFN and RBV, who are the most difficult category of patients with HCV infection to treat successfully. We expect to receive final SVR data from the ongoing registration clinical trials for telaprevir during the second and third quarters of 2010 and expect to submit the NDA for telaprevir in the second half of 2010. If we obtain positive results from the ongoing registration program and are able to obtain approval of telaprevir on our current timeline, we plan to initiate sales of telaprevir in the United States in 2011.

Become a fully-capable biopharmaceutical company. In order to become a fully-capable biopharmaceutical company, we believe we need to build and establish an effective sales and marketing organization to augment our existing research capabilities along with the late-stage development organization and third-party manufacturing relationships that we have built over the last several years. Although we have been expanding our commercial infrastructure, we will need to further expand these capabilities in order to effectively launch telaprevir and to position our company for the future.

Invest in research and early and mid-stage development programs. We intend to continue to invest significant resources in research programs and early-stage and mid-stage clinical development programs as part of our strategy to develop drug candidates in therapeutic areas with significant unmet need. In 2010, we expect to conduct Phase 2a clinical trials involving drug candidates, which we have developed internally or acquired through business development activities, that are intended to address significant unmet needs in HCV, CF, rheumatoid arthritis and epilepsy. We expect to continue focusing our research activities toward therapies addressing serious diseases, because we believe these therapies have the potential to deliver the greatest value for patients, physicians and the health care system.

Capitalize on collaboration arrangements and business development opportunities. Collaborations have provided us with financial support and other valuable resources for our development and research programs, and business development opportunities have provided us with drug candidates and important research resources that have contributed to a number of the drug candidates in our current development pipeline. We plan to continue to rely on collaborators to support, develop and commercialize some of our drug candidates either worldwide or in markets in which we are not concentrating our resources. We also opportunistically seek to license and acquire drugs, drug candidates and other technologies that have the potential to strengthen our pipeline, drug discovery platform or commercial opportunities.

Table of Contents

DRUG CANDIDATES

HCV Infection

Telaprevir (VX-950) (investigational oral HCV protease inhibitor for the treatment of HCV infection)

Telaprevir, our lead drug candidate, is an orally-administered hepatitis C protease inhibitor that is being evaluated in treatment-naïve and treatment-failure patients with genotype 1 HCV infection in combination with peg-IFN and RBV. Telaprevir is designed to inhibit the NS3-4A serine protease, an enzyme necessary for HCV replication. The United States Food and Drug Administration, or FDA, has granted "Fast Track" designation to telaprevir. We have completed dosing of all study drugs in the registration program for telaprevir. Assuming the successful completion this year of our registration program for telaprevir, we intend to submit an NDA for telaprevir in the United States in the second half of 2010 and to initiate commercial sales of telaprevir in the United States in 2011. In addition to the current registration program, we also are planning to initiate a Phase 2a clinical trial to evaluate telaprevir in combination with VX-222, a polymerase inhibitor, with and without peg-IFN and RBV.

We have collaboration agreements relating to telaprevir with Janssen Pharmaceutica, N.V., or Janssen, a Johnson & Johnson company, and Mitsubishi Tanabe Pharma Corporation, or Mitsubishi Tanabe. Pursuant to these agreements, Janssen will be responsible for the commercialization of telaprevir, including the manufacture of its own commercial supply of telaprevir, outside of North America and the Far East. Mitsubishi Tanabe will be responsible for the commercialization of telaprevir, including the manufacture of its own commercial supply of telaprevir, in Japan and specified other countries in the Far East. Telaprevir was discovered in our collaboration, now ended, with Eli Lilly and Company. We expect to pay Eli Lilly certain royalties on future sales of telaprevir, if approved.

Background: Prevalence and Treatment of Hepatitis C Virus Infection

HCV infection causes an inflammation of the liver called chronic hepatitis. This condition can progress to scarring of the liver, called fibrosis, or more advanced scarring, called cirrhosis. Patients with cirrhosis may go on to develop liver failure or other complications of cirrhosis, including liver cancer. The World Health Organization has reported 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.

The World Health Organization has estimated that about 170 million people are chronically infected with HCV worldwide and that an additional 3 million to 4 million people are infected each year. The Centers for Disease Control and Prevention have estimated that approximately 3.2 million people in the United States are chronically infected with HCV.

Our clinical development activities related to telaprevir are focused on genotype 1 HCV infection, which is the most prevalent form of HCV infection in the United States, the European Union and Japan. We believe that approximately 2.6 million patients in the United States have genotype 1 HCV infection. We believe that these patients include approximately 750,000 patients who already have been diagnosed with genotype 1 HCV infection and 1.8 million patients who remain undiagnosed.

In addition to being the most prevalent form of HCV infection, infection with genotype 1 HCV is the most difficult to treat of the primary HCV genotypes. The current standard treatment for infection with genotype 1 HCV, which was first approved in 2001, is a combination of peg-IFN and RBV, generally administered for 48 weeks. This treatment regimen is associated with significant side-effects, including fatigue, flu-like symptoms, rash, depression and anemia. Among patients who begin treatment, a significant percentage of patients infected with genotype 1 HCV fail to achieve a long-term sustained response to therapy. For example, on an intent-to-treat basis, 41% and 46%, respectively, of treatment-naïve patients in the standard therapy arms of our Phase 2b clinical trials known as PROVE 1 and PROVE 2 achieved an SVR. In another clinical trial conducted by another

Table of Contents

company, involving approximately 3,070 treatment-naïve patients in the United States infected with genotype 1 HCV, between 38% and 41% of patients receiving peg-IFN and RBV achieved an SVR. We believe that there are over 250,000 patients infected with genotype 1 HCV in the United States who have failed to achieve an SVR after therapy with peg-IFN and RBV.

Telaprevir Clinical Development

The three clinical trials in our registration program are ADVANCE and ILLUMINATE, Phase 3 clinical trials of telaprevir-based treatment regimens in treatment-naïve patients with genotype 1 HCV infection, and REALIZE, a Phase 3 clinical trial of telaprevir-based treatment regimens in treatment-failure patients with genotype 1 HCV infection. Dosing of all study groups in these three clinical trials has been completed. SVR data are expected from ADVANCE in the second quarter of 2010 and from ILLUMINATE and REALIZE in the third quarter of 2010.

The ADVANCE trial is a 3-arm double-blinded placebo-controlled clinical trial that enrolled approximately 1,050 patients with genotype 1 HCV infection. ADVANCE contains two telaprevir-based treatment arms, one in which patients receive 12 weeks of telaprevir-based triple combination therapy and one in which patients receive 8 weeks of telaprevir-based triple combination therapy, in each case taking peg-IFN and RBV for a period of time after completing telaprevir dosing. Patients in both of the telaprevir-based treatment arms who meet extended rapid viral response criteria, or eRVR, complete all treatment after 24 weeks, while patients who are responding to treatment but do not meet the eRVR criteria continue receiving peg-IFN and RBV for a total of 48 weeks of therapy. To achieve an eRVR a patient must have undetectable HCV RNA levels at the end of week 4 and week 12 after the start of treatment.

ADVANCE Clinical Trial Design

Table of Contents

ILLUMINATE is a Phase 3 clinical trial, which includes evaluation of 24-week and 48-week total treatment durations in treatment-naïve patients infected with genotype 1 HCV who achieve an eRVR in response to telaprevir-based treatment regimens. This clinical trial is a randomized, open-label trial that enrolled approximately 500 patients. ILLUMINATE is designed to supplement SVR data obtained from the ADVANCE trial to evaluate the benefits and risks, for patients who achieve an eRVR, of extending total treatment duration from 24 to 48 weeks.

ILLUMINATE Clinical Trial Design

The REALIZE trial is a 3-arm clinical trial of telaprevir-based treatment regimens in approximately 650 patients with genotype 1 HCV infection who failed to achieve an SVR after treatment with peg-IFN and RBV alone. One treatment arm is evaluating a lead-in strategy in which patients receive four weeks of pre-treatment with peg-IFN and RBV prior to starting telaprevir. REALIZE is being managed by our collaborator Tibotec Pharmaceuticals Ltd., which is a Johnson & Johnson company and an affiliate of Janssen. REALIZE includes the following patient groups:

null responders those patients who experienced less than a 2 $\log_{10}$ reduction in HCV RNA levels at week 12 of prior therapy;

partial responders those patients who experienced at least a 2 $\log_{10}$ reduction in HCV RNA levels at week 12 of prior therapy, but who failed to achieve undetectable HCV RNA levels by week 24; and

relapsers those patients who experienced undetectable HCV RNA levels at the completion of at least 42 weeks of prior treatment, but who relapsed after treatment ended.

REALIZE Clinical Trial Design

Table of Contents

Telaprevir Clinical Data

PROVE Phase 2b Clinical Trials

We have completed three Phase 2b clinical trials of telaprevir-based combination therapy in patients infected with genotype 1 HCV, referred to as the PROVE trials. The PROVE trials enrolled an aggregate of approximately 580 treatment-naïve patients and 440 treatment-failure patients. The SVR rates on an intent-to-treat basis for patients in the 24-week telaprevir-based treatment arms and the control arms of PROVE 1 and PROVE 2, the two Phase 2b clinical trials that evaluated treatment-naïve patients, are set forth in the table below:

	PROVE 1	PROVE 2
24-week telaprevir-based treatment arm:		
telaprevir in combination with peg-IFN and RBV for 12 weeks, followed by peg-IFN and RBV alone for 12 weeks	61%	69%
48-week control arm:		
48 weeks of therapy with peg-IFN and RBV	41%	46%

PROVE 3 was a Phase 2b clinical trial that evaluated telaprevir-based treatment of patients who had failed at least one course of treatment with peg-IFN and RBV, the current standard of care. The SVR rates on an intent-to-treat basis for patients in the 24-week telaprevir-based treatment arm, the 48-week telaprevir-based treatment arm and the control arm of PROVE 3 are set forth in the table below. Non-responders are patients who were not responsive to prior treatment and consist of a mixture of null and partial responders. Relapsers are patients who had viral rebound during the period following prior treatment. Breakthroughs are patients who experienced a viral rebound during prior treatment.

	Non-responders	Relapsers	Breakthroughs	Total
24-week telaprevir-based triple-therapy treatment arm:				
telaprevir in combination with peg-IFN and RBV for 12 weeks, followed by peg-IFN and RBV alone for 12 weeks	39% (n=66)	69% (n=42)	57% (n=7)	51% (n=115)
48-week telaprevir-based treatment arm:				
telaprevir in combination with peg-IFN and RBV for 24 weeks, followed by peg-IFN and RBV alone for 24 weeks	38% (n=64)	76% (n=41)	50% (n=8)	52% (n=113)
48-week control arm:				
48 weeks of therapy with peg-IFN and RBV	9% (n=68)	20% (n=41)	40% (n=5)	14% (n=114)

The adverse event profile of telaprevir generally was consistent across our Phase 2 clinical trials, which have principally involved clinical trial sites in North America and Europe. Safety data from our Phase 2 clinical trials indicated that the most common adverse events, regardless of treatment assignment, were fatigue, rash, headache and nausea. The most common adverse events reported more frequently in patients receiving telaprevir than in the control arms were gastrointestinal events, skin events rash and pruritus and anemia. There have been reports of severe rashes in clinical trials involving telaprevir-based treatments, including several reports from the clinical trials being conducted by Mitsubishi Tanabe in Japan, where telaprevir is being evaluated in Phase 3 clinical trials in combination with peg-IFN and RBV. Rash resulted in treatment discontinuations in the telaprevir-based treatment arms in approximately 7% of patients in PROVE 1 and PROVE 2 and 5% of patients in PROVE 3. Other adverse events reported in our Phase 2 clinical trials generally were similar in type and frequency to those seen with peg-IFN and RBV treatment. Our ongoing registration program includes a rash management program that was developed based on the information from the PROVE 1 and PROVE 2 clinical trials and first implemented in our PROVE 3 clinical trial.

Table of Contents

Additional Phase 2 Clinical Trials of Telaprevir

In October 2009, we announced data from the C208 trial, which was an exploratory open-label clinical trial that enrolled 161 treatment-naïve patients infected with genotype 1 HCV in Europe. The purpose of the C208 trial was to compare twice-daily dosing regimens of telaprevir 1,125 mg every 12 hours in combination with peg-IFN and RBV, with three-times daily dosing regimens 750 mg every 8 hours in combination with peg-IFN and RBV. A three-times daily dosing regimen is being used in the ongoing registration program for telaprevir and has also been used in the other clinical trials for telaprevir.

In the C208 trial, patients received telaprevir, peg-IFN and RBV for 12 weeks followed by an additional period of therapy of peg-IFN and RBV alone in a response-guided trial design. The design is response-guided because the time period during which a patient remains on therapy with peg-IFN and RBV alone after completion of therapy with a combination of telaprevir, peg-IFN and RBV is adjusted depending on the nature of the patient's early response to treatment. Patients who achieved at week 4 HCV RNA levels of less than 25 IU/mL, which is undetectable in the test used and is referred to as a rapid viral response or RVR, and also demonstrated undetectable HCV RNA through week 20, were able to stop all treatment after 24 weeks. Patients who did not meet the response-guided criteria were treated for a total of 48 weeks. 18% of patients across the treatment arms were required to continue treatment for 48 weeks.

The following table summarizes the RVR and SVR data on an intent-to-treat basis from the C208 trial.

Telaprevir Dosing	Combination Therapy	Total Number of Patients	RVR (undetectable at week 4 on treatment)	SVR (undetectable 24 weeks after end-of-treatment)
1,125 mg every 12 hours	alfa-2a (PEGASYS)/RBV	40	83% (n=33)	83% (n=33)
1,125 mg every 12 hours	alfa-2b (PEGINTRON)/RBV	39	67% (n=26)	82% (n=32)
750 mg every 8 hours	alfa-2a (PEGASYS)/RBV	40	80% (n=32)	85% (n=34)
750 mg every 8 hours	alfa-2b (PEGINTRON)/RBV	42	69% (n=29)	81% (n=34)

The frequency and severity of adverse events and the rate of treatment discontinuations were similar to those reported in prior telaprevir trials. The most common adverse events reported in patients in this clinical trial were pruritis, nausea, rash, anemia, flu-like illness, fatigue and headache, and the adverse events were similar overall across the patient groups receiving three-times daily dosing and those receiving twice-daily dosing. Serious adverse events leading to permanent treatment discontinuation of all drugs occurred in 5% of patients and were mainly related to rash, which resulted in discontinuation of 4 out of 161, or 3%, of patients, and anemia, which resulted in discontinuation of 3 out of 161, or 2%, of patients.

We also provided interim data in 2009 from an exploratory clinical trial, referred to as the 107 Trial, in patients from the control arms of the PROVE 1, PROVE 2 or PROVE 3 clinical trials who did not achieve an SVR. We expect to present final data from the 107 Trial during 2010.

Mitsubishi Tanabe Clinical Program

Mitsubishi Tanabe has three ongoing Phase 3 trials of telaprevir-based combination therapy in approximately 300 treatment-naïve and treatment-failure patients with HCV infection in Japan. Mitsubishi Tanabe has completed the telaprevir dosing portion of these Phase 3 clinical trials.

Table of Contents

VX-222 (investigational oral HCV polymerase inhibitor for the treatment of HCV infection)

HCV polymerase inhibitors, including our HCV polymerase inhibitor VX-222, are direct-acting antiviral agents that inhibit the replication of HCV, but through a mechanism distinct from HCV protease inhibitors such as telaprevir. VX-222 was evaluated by ViroChem Pharma Inc., or ViroChem, in Phase 1 clinical trials prior to our acquisition of ViroChem in March 2009. In this Phase 1 viral kinetics clinical trial, which involved five treatment-naïve patients with genotype 1 HCV infection, VX-222 dosed at 750 mg twice daily resulted in a median 3.7 $\log_{10}$ decrease in HCV RNA equivalent to a 5,000-fold reduction in virus in the blood at the end of three days of dosing. The results were consistent from patient to patient, and across HCV genotype 1 subtypes. We recently reported interim data from a multiple-dose Phase 1b viral kinetic clinical trial of VX-222 that we are conducting to evaluate the antiviral activity, safety, tolerability and pharmacokinetics of VX-222 in patients with genotype 1 HCV infection. Interim results were consistent with the findings of the previously-conducted three-day viral kinetics clinical trial. No serious adverse events were reported in this trial.

We are engaged in late-stage discussions with the FDA and other international regulatory authorities, regarding the initiation of a Phase 2a combination trial of telaprevir and VX-222. This clinical trial is expected to begin in the first quarter of 2010 and to evaluate SVR rates using multiple regimens of telaprevir/VX-222-based therapy in patients with HCV infection.

Additional HCV Research Activities and Development Programs

In addition to our development activities focused on telaprevir and VX-222, we are conducting a number of earlier-stage research and development activities aimed at identifying compounds that have advantageous characteristics for potential use against HCV infection. As we obtain new data and scientific, business and commercial insights into our own drug candidates and the drug candidates being developed by other companies, we may periodically change our focus and priority with respect to the drug candidates we are developing and the research programs we are pursuing. We currently consider VX-759, a second polymerase inhibitor that we acquired in our ViroChem acquisition, to be a back-up drug candidate to VX-222. VX-759 has been evaluated in Phase 1 clinical trials, and there are no ongoing clinical trials for VX-759. VX-985, an investigational HCV protease inhibitor that we discovered, is currently in Phase 1 clinical development. VX-813, another investigational HCV protease inhibitor, is no longer in development. We have an ongoing research program directed at identifying NS5A inhibitors, a third class of specifically targeted anti-viral compounds that we believe may be useful in the treatment of HCV infection.

Cystic Fibrosis

Cystic fibrosis is a genetic disorder that affects about 30,000 people in the United States and 70,000 worldwide. The drug candidates that we are developing for CF were selected because of their potential to address the underlying cause of CF by increasing the function of a defective protein in CF patients, known as the cystic fibrosis transmembrane conductance regulator, or CFTR. While CF is a systemic disease, progressive loss of lung function is the primary cause of increased mortality in patients with CF. Abnormally thick mucus in the lungs of patients with CF leads to chronic lung infections, lung inflammation and progressive decline in lung function. Some patients with CF also experience problems with digestion, due to a lack of CFTR function in the pancreas, resulting in the need for enzyme replacement therapy. According to the Cystic Fibrosis Foundation in 2008, the predicted median survival for patients with cystic fibrosis is 37 years. The underlying cause of CF is a genetically inherited deficiency in the production or activity of the CFTR protein. The CFTR protein is involved in controlling the movement of chloride ions into and out of cells in the lung, sweat glands, pancreas and other organs.

Table of Contents

CF develops when neither of the two copies of the *CFTR* gene, referred to as alleles, produce sufficient functional CFTR protein. There are numerous mutations in the *CFTR* gene that result in CF, including the G551D mutation and the F508del mutation. The G551D mutation results in a defect known as a gating defect, in which the CFTR protein reaches the cell surface but does not efficiently transport chloride ions across the cell membrane. The F508del mutation results in a defect known as a trafficking defect, in which the CFTR protein does not reach the cell surface in sufficient quantities.

According to the 2007 Cystic Fibrosis Foundation Patient Registry Annual Data Report in the United States, approximately 4% of patients with CF have the G551D mutation on at least one allele, 49% of patients with CF have the F508del mutation on both alleles and an additional approximately 38% of patients with CF have the F508del mutation on one allele.

There is no available therapy that improves the function of defective CFTR proteins. Instead, available treatments for CF pulmonary disease focus on improving mucus clearance from the lungs as well as treating lung infections and inflammation. Improved mucus clearance is sought through physical therapy, inhalation of a mucus thinning drug such as Pulmozyme, or inhalation of hypertonic saline. Lung infections are treated with inhaled and systemic antibiotics while inflammation is treated with anti-inflammatory agents like ibuprofen. In addition, the majority of CF patients take pancreatic enzyme supplements to assist with food absorption in digestion.

FEV_1, a test of the amount of air that an individual can exhale in one second, is the lung function test most commonly used to monitor CF disease progression, which is characterized by progressive decreases in FEV_1 values compared to FEV_1 values observed in healthy individuals. The FEV_1 test has been used as an efficacy end-point during testing of the currently approved pulmonary drugs for the treatment of CF. Since CF is a chronic disease, pivotal clinical trials of CF drug candidates have involved the measurement of FEV_1 values over a number of months. Mean increases in percent predicted FEV_1 of between 5% and 10% over 24-week periods have been observed in the pivotal clinical trials of the mucus thinning drugs and antibiotics most widely used for the management of CF.

We are conducting clinical trials of two drug candidates, VX-770 and VX-809, that were selected because of their potential to improve the function of defective CFTR proteins in patients with CF. We discovered VX-770 and VX-809 in our research collaboration with The Cystic Fibrosis Foundation Therapeutics Incorporated, or CFFT, and with the support and participation of the Cystic Fibrosis Foundation. We hold worldwide development and commercialization rights to VX-770 and VX-809, but we will pay royalties to CFFT on any future sales of VX-770 or VX-809.

VX-770 (investigational oral CFTR potentiator for the treatment of cystic fibrosis)

VX-770 is an investigational oral drug candidate that was selected because of its potential to increase chloride ion transport across cell membranes by partially restoring the activity of defective CFTR protein. In May 2009, we initiated a registration program, referred to as ENDEAVOR, for VX-770. The VX-770 registration program focuses on patients with the G551D mutation. The registration program consists of three clinical trials.

The primary clinical trial, which is referred to as STRIVE, is a Phase 3 clinical trial of VX-770 that enrolled approximately 170 patients 12 years and older with the G551D mutation on at least one of the patient's two *CFTR* genes, or alleles. In this randomized, placebo-controlled, double-blind, parallel-group clinical trial, patients will receive either VX-770 or placebo for 48 weeks. The second clinical trial, which is referred to as ENVISION, is a Phase 3 clinical trial of VX-770 in patients between 6 to 11 years of age with the G551D mutation on at least one allele. ENVISION is a two-part, randomized, placebo-controlled, double-blind, parallel-group clinical trial of VX-770. We have completed part 1 of ENVISION, which evaluated single-dose pharmacokinetics to determine the dose selection for children ages 6 to 11. We expect that Part 2 of the ENVISION trial will enroll approximately 30 patients who will receive either VX-770 or placebo for 48 weeks. The primary endpoint for the STRIVE and ENVISION clinical trials is absolute change from baseline in FEV_1

Table of Contents

through week 24. Additional FEV_1 measurements will be taken through 48 weeks as a secondary endpoint. Secondary endpoints, including sweat chloride levels, will be measured to evaluate the effectiveness of VX-770 in improving the function of the defective CFTR protein.

The third clinical trial, which is referred to as DISCOVER, is a Phase 2 exploratory clinical trial of VX-770 that enrolled approximately 120 patients with CF who are 12 years and older and with the F508del mutation on both alleles. In this randomized, placebo-controlled, double-blind, parallel-group trial, patients will receive either VX-770 or placebo for 16 weeks. The primary endpoints of the DISCOVER clinical trial are safety and change from baseline in FEV_1 through week 16. Additional secondary endpoints, including sweat chloride levels, will be measured to evaluate the effectiveness of VX-770 in improving the function of the defective CFTR protein. We currently anticipate that further clinical trials in patients homozygous for the F508del mutation will involve a combination of VX-770 and VX-809.

STRIVE and DISCOVER are fully-enrolled and we expect to complete enrollment in ENVISION in the first half of 2010. If our registration program for VX-770 is successful and completed on the timeline that we currently anticipate, we could submit an NDA for VX-770 in the second half of 2011.

Completed Phase 2a Clinical Trial of VX-770

We have completed a Phase 2a clinical trial of VX-770 that enrolled 39 patients with the G551D mutation on at least one allele, 20 of whom were enrolled in Part 1 of the clinical trial and 19 of whom were enrolled in Part 2 of the clinical trial. Patients in Part 1 of this clinical trial were dosed with VX-770 or placebo over 14 day periods. In Part 2 of this Phase 2a clinical trial, patients were dosed over 28 days in the following three arms: eight patients received 150 mg of VX-770 twice daily; seven patients received 250 mg of VX-770 twice daily; and four patients received a placebo twice daily.

Safety (primary endpoint)

The primary endpoint of this VX-770 Phase 2a clinical trial was safety. In Part 1, observed adverse events were similar between VX-770 and placebo treatment over the dosing period. Two serious adverse events were observed in one patient in Part 1, but were not attributed to VX-770. In Part 2 of this clinical trial, no serious adverse events were reported and no patients discontinued treatment over the 28-day dosing period. Also in Part 2, all reported adverse advents were mild or moderate in severity.

Lung Function and CFTR Protein Function (secondary endpoints)

In this VX-770 Phase 2a clinical trial, we measured secondary endpoints of lung function and CFTR protein function. We measured changes in lung function using FEV_1. CFTR activity was evaluated through measurements of sweat chloride levels and nasal potential difference, or NPD. Elevated sweat chloride levels high levels of salt in sweat occur in CF patients and result directly from defective CFTR activity in epithelial cells in the sweat ducts. Patients with CF typically have elevated sweat chloride levels that are in excess of 60 mmol/L, compared to normal values of less than 40 mmol/L. NPD assesses several aspects of ion channel activity by measuring voltage changes across the nasal epithelia and is used as a direct measure of CFTR activity and chloride ion movement in upper airway epithelial cells. Typical assessments of patient NPD show very low CFTR-mediated chloride ion transport in the nasal passage of patients with CF.

In Part 1 of the Phase 2a clinical trial of VX-770, the eight patients who received 150 mg twice-daily over 14 days had a 10.1% improvement in lung function as measured by an increase in FEV_1. In these patients, sweat chloride levels had a mean decrease of 42.3 mmol/L from a mean baseline of 95.5 mmol/L over the 14-day dosing period. The NPD component decreased by 5.4 mV, indicating increased CFTR function. There were no statistically significant changes in any of the efficacy measures

Table of Contents

in the placebo arms of Part 1. The four patients receiving placebo in Part 1 showed a slight decrease in FEV_1, no notable change in sweat chloride levels and a -1.74 mV change in NPD.

A summary of data regarding lung function and biomarkers of the CFTR protein function, including "p-values" from Part 2 of this Phase 2a clinical trial, is set forth in the table below. The result of statistical testing is often defined in terms of a "p-value," with a p-value of 0.05 or less generally considered to represent a statistically significant difference.

Number of Patients	Treatment Arm	FEV_1 Mean Increase from Baseline at Day 28 (p-value)	Sweat Chloride Mean Decrease from Baseline at Day 28 (p-value)	Sweat Chloride Baseline	NPD Mean Decrease from Baseline at Day 28 (p-value)
8	150 mg	11.6% (p<0.01)	-52.8 mmol/L(p<0.01)	102 mmol/L	-4.3 mV (p<0.05)
7	250 mg	7.4% (p<0.05)	-32.4 mmol/L (p<0.05)	94.9 mmol/L	-10.1 mV (p<0.05)
4	Placebo	7.0% (p=0.13)	+4.8 mmol/L (p=0.38)	98.3 mmol/L	+0.3 mV (p=0.88)

The pattern of FEV_1 response in the VX-770 arms was characterized by a rapid and sustained increase in FEV_1 through 28 days. The increase in FEV_1 in the placebo arm was not considered statistically significant.

VX-809 (investigational oral CFTR corrector compound for the treatment of CF)

We are evaluating VX-809, an oral corrector compound that was selected because of its potential to increase the concentration of CFTR proteins on cell surfaces, in patients with the F508del mutation, a mutation that results in a trafficking defect. *In vitro*, studies of correctors have suggested that these compounds can restore function of defective F508del CFTR protein, with increased trafficking of F508del CFTR protein to the cell surface and enhanced gating activity of F508del CFTR protein on the cell surface.

We recently completed a Phase 2a, 28-day clinical trial of VX-809 as a single agent in 89 patients 18 years or older with the F508del mutation on both alleles. This Phase 2a clinical trial was a randomized, double-blind, placebo-controlled, multiple dose clinical trial. Patients received one of four doses of VX-809, or placebo, in addition to standard therapies for 28 days. The trial was designed primarily to evaluate the safety and tolerability of VX-809. Multiple secondary endpoints were utilized to determine any effect of VX-809 on CFTR protein function and lung function.

Based on a preliminary analysis of the data from the trial, VX-809 was well-tolerated through 28 days of 25 mg, 50 mg, 100 mg and 200 mg once-daily dosing. In the trial, one patient discontinued treatment in each of the VX-809 treatment arms due to adverse events. Respiratory-related adverse events were the most commonly reported adverse event in the trial. Safety and tolerability were the primary endpoints of the trial, and a detailed safety analysis is ongoing.

We also evaluated several secondary endpoints in the Phase 2a clinical trial. In the trial, there was a statistically significant decline in sweat chloride at both the 100 mg and 200 mg once-daily doses, suggesting that the activity of the CFTR protein was increased in patients during dosing. Additionally, we observed a dose response in change in sweat chloride across the four dose groups. A summary of the preliminary data regarding sweat chloride levels from this Phase 2a clinical trial is set forth in the table below. The patients' mean baseline sweat chloride levels were approximately 100 mmol/L, which is consistent with sweat chloride measurements of patients with severe CF.