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Vertex Outlines 2015 Business Priorities to Support the Development, Approval and Launch of New Medicines for the Treatment of People with Cystic Fibrosis

-Priority Review granted for combination of lumacaftor and ivacaftor in people with cystic fibrosis ages 12 and older who have two copies of the F508del mutation; PDUFA date of July 5, 2015-

-More than 3,700 people with CF expected to be eligible to receive KALYDECO by end of 2015 supporting continued growth in KALYDECO global revenues; 2015 KALYDECO net revenue guidance of $560 - $580 million-

-Pivotal Phase 3 program of VX-661 in combination with ivacaftor to begin in February in people with cystic fibrosis who have either one or two copies of the F508del mutation-

SAN FRANCISCO--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq:VRTX) today outlined 2015 business priorities to support the development, approval and launch of new medicines that treat the underlying cause of cystic fibrosis (CF). The company also provided 2015 guidance for KALYDECO® (ivacaftor) net revenues and for non-GAAP operating expenses. These updates were made in conjunction with the 33rd Annual J.P. Morgan Healthcare Conference that begins tomorrow in San Francisco. Vertex's Chairman, President and Chief Executive Officer, Jeffrey Leiden, M.D., Ph.D., will discuss the company's continued execution of its corporate strategy and 2015 priorities as part of a live presentation on Monday, January 12 at 9:30 a.m. PT (12:30 p.m. ET). The presentation will be webcast on Vertex's website, www.vrtx.com.

"Vertex enters a year where the potential approval and launch of the combination of lumacaftor and ivacaftor, and continued geographic and label expansion for KALYDECO, are expected to significantly increase the number of people treated with our medicines," said Dr. Leiden. "We enter 2015 with a strong cash position of approximately $1.4 billion, which, when combined with continued revenue growth, will allow us to invest in key internal and external opportunities in CF and other diseases to bolster our pipeline and position the company to advance other transformative medicines in the coming years."

Vertex today provided the following updates:

KALYDECO (ivacaftor)

At the start of 2014, more than 2,200 people with CF ages 6 and older with the G551D mutation were eligible for treatment with KALYDECO in North America, Europe and Australia. Following the expansion of the KALYDECO label throughout 2014, more than 3,100 people ages 6 and older are currently eligible for treatment with KALYDECO, including people with one of eight gating mutations and, in the United States, people with the R117H mutation. Vertex currently expects that by the end of 2015, more than 3,700 people may be eligible for treatment with KALYDECO, including children ages 2 to 5 and, in Europe, adults with the R117H mutation.

Vertex today announced that its New Drug Application (NDA) for the use of ivacaftor in children ages 2 to 5 who have the G551D or one of the eight additional gating mutations was accepted for filing by the Food and Drug Administration (FDA), and a target review date of March 17, 2015 was set under the Prescription Drug User Fee Act (PDUFA) for the FDA's approval decision.

In Europe, discussions are ongoing regarding reimbursement for patients with non-G551D gating mutations. Additionally, a Marketing Authorization Application (MAA) variation for ivacaftor in people ages 18 and older with the R117H mutation and an MAA line extension for ivacaftor in children ages 2 to 5 with gating mutations have both been validated by the European Medicines Agency (EMA). Validation indicates that the application is complete and starts the regulatory review process by the Committee for Medicinal Products for Human Use (CHMP). Following its review, the CHMP issues an opinion that is then considered by the European Commission, which has the authority to approve medicines for the European Union. If approved, Vertex would then begin the country-by-country reimbursement approval process.

In Australia, KALYDECO was listed on the Pharmaceutical Benefits Scheme (PBS) as of December 1, 2014, which is intended to provide reimbursement for all eligible patients ages 6 and older with the G551D or other gating mutations. Patients in Australia have now begun to receive treatment with KALYDECO.

Lumacaftor in Combination with Ivacaftor in People with Two Copies of the F508del Mutation

Vertex today announced that the FDA has accepted its NDA for the combination of lumacaftor and ivacaftor in people with CF ages 12 and older who have two copies of the F508del mutation. The FDA granted Vertex's request for Priority Review, with a target review (PDUFA) date of July 5, 2015 for the FDA's approval decision. In Europe, the MAA for this combination regimen has been validated by the EMA and is under review by the CHMP. The CHMP granted Vertex's request for Accelerated Assessment of the MAA, which is given to new medicines of major public health interest and shortens the review time from approximately 210 to 150 days for the CHMP to give an opinion following the start of the review. The CHMP opinion is then reviewed by the European Commission, which generally issues a final decision within three months. If approved, Vertex would then begin the country-by-country reimbursement approval process. In 2015, Vertex also plans to submit applications for regulatory approval of the combination of lumacaftor and ivacaftor in Canada and Australia. There are approximately 22,000 people with CF ages 12 and older who have two copies of the F508del mutation in North America, Europe and Australia, including approximately 8,500 in the United States and 12,000 in Europe.

Vertex also plans to initiate a study of lumacaftor in combination with ivacaftor in children ages 6 to 11 who have two copies of the F508del mutation in the first half of 2015. The study is expected to evaluate the combination regimen as part of a single-arm, open-label design in approximately 50 children. The primary endpoint of the study will be safety and pharmacokinetics.

VX-661 in Combination with Ivacaftor in People with One or Two Copies of the F508del Mutation

Vertex is currently conducting a 12-week Phase 2 study of VX-661 in combination with ivacaftor in people with CF who have two copies of the F508del mutation. Vertex completed enrollment in the study in October 2014. The study enrolled approximately 20 patients who received placebo and approximately 20 patients who received one of two doses of VX-661 (50 mg q12h or 100 mg QD) in combination with ivacaftor (150 mg q12h). The primary endpoint of the study is safety, and additional secondary endpoints will evaluate the pharmacokinetics and efficacy of VX-661. 12-week data from this study are expected in the first quarter of 2015.

Vertex plans to initiate a Phase 3 pivotal program of VX-661 in combination with ivacaftor in February. The initiation of the Phase 3 program is based on safety and efficacy data from Phase 2 studies of VX-661, including interim data from the ongoing 12-week Phase 2 study and previously completed studies of VX-661 in combination with ivacaftor in people with two copies of the F508del mutation and in people with one copy of the F508del mutation and one copy of the G551D mutation, and recent regulatory discussions regarding the design of the Phase 3 program. The program will consist of four studies that will evaluate VX-661 dosed as 100 mg once daily (QD) in combination with ivacaftor dosed as 150 mg every 12 hours (q12h). The first of the studies is expected to begin in February. Additional details on each of the four planned studies are provided below:

- **Two Copies of the F508del Mutation:** In February, Vertex plans to begin a Phase 3 study to evaluate the combination of VX-661 and ivacaftor in people ages 12 and older who have two copies of the F508del mutation. The primary endpoint of the study will be absolute change in $ppFEV_1$ through six months of treatment versus placebo. The study will enroll approximately 500 patients in North America and Europe. The majority of the study sites will be in Europe, including the countries of Denmark, France, Germany, the Republic of Ireland, Italy, the Netherlands, Spain, Sweden, Switzerland and the United Kingdom.
- **One Copy of the F508del Mutation and a Second Mutation that Results in a Gating Defect in the CFTR Protein:** In the second quarter of 2015, Vertex plans to begin a Phase 3 study to evaluate the combination of VX-661 and ivacaftor in people ages 12 and older who have one copy of the F508del mutation and a second mutation that results in a gating defect in the CFTR protein. The primary endpoint of the study will be absolute change in $ppFEV_1$ through eight weeks of treatment with VX-661 and ivacaftor versus ivacaftor alone. The study will enroll approximately 200 patients in North America and Europe.
- **One Copy of the F508del Mutation and a Second Mutation That Results in Residual CFTR Function:** In the second quarter of 2015, Vertex plans to begin a Phase 3 study to evaluate the combination of VX-661 and ivacaftor in people ages 12 and older who have one copy of the F508del mutation and a second mutation that results in residual CFTR function. This study will also evaluate ivacaftor dosed without VX-661. The primary endpoint of the study will be absolute change in $ppFEV_1$ through eight weeks of treatment as part of a crossover design. The study will enroll approximately 300 patients in North America and Europe.
- **One Copy of the F508del Mutation and A Second Mutation That Results in Minimal CFTR Function:** In the second quarter of 2015, Vertex plans to begin a Phase 3 study to evaluate the combination of VX-661 and ivacaftor in people ages 12 and older who have one copy of the F508del mutation and a second mutation that results in minimal CFTR function. The study will initially enroll approximately 120 patients, and the primary endpoint will be absolute change in $ppFEV_1$ through 12 weeks of treatment versus placebo. Expansion of the study to an additional approximately 150 patients will depend on an interim futility analysis of efficacy data from the initial approximately 120 patients.

Next-generation Correctors

Vertex has multiple next-generation correctors in the lead-optimization stage of research and expects to begin clinical development of a next-generation corrector in 2015. *In vitro* data showed that a triple combination of VX-661, ivacaftor and a next-generation corrector resulted in increased chloride transport in human bronchial epithelial cells with one or two copies of the F508del mutation, as compared to the use of a single corrector in combination with ivacaftor.

Research and Early-stage Development Programs

In addition to its ongoing CF research activities, Vertex is advancing multiple additional research and early development programs aimed at the discovery of future transformative medicines for serious diseases, with a focus on specialty markets. The company's research and early development efforts are focused on oncology and multiple neurological diseases. Vertex expects multiple compounds in oncology and neurological diseases to be in clinical development in 2015.

Financial

"We expect 2015 to be a year of rapid and significant growth in revenues based on treating many more people with CF following the potential approval and launch of the combination of lumacaftor and ivacaftor and further label and geographic expansion for KALYDECO," said Ian Smith, Executive Vice President and Chief Financial Officer for Vertex. "As our revenues increase, we are committed to managing our operating expense to support high future operating margins and earnings growth."

Vertex today provided the following financial outlook and will provide complete financial guidance on its year-end conference call on January 28, 2015:

- Vertex entered 2015 with approximately $1.4 billion in cash, cash equivalents and marketable securities. In July 2014, Vertex entered into a credit agreement that provides for a secured loan of up to $500 million, $300 million of which Vertex received in July 2014 and is currently outstanding.
- Vertex expects total 2015 KALYDECO net revenues of $560 to $580 million. Vertex expects to report total 2014 KALYDECO net revenues of approximately $460 million and fourth quarter KALYDECO net revenues of approximately $120 million. Anticipated 2015 KALYDECO net revenues reflect:
    - Use of KALYDECO by eligible patients in Australia following the completion of reimbursement discussions in late 2014
    - Use of KALYDECO in people in the United States with the R117H mutation following FDA approval in late 2014
    - The completion of reimbursement discussions for gating mutations in certain European countries
    - Use of KALYDECO in children with CF ages 2 to 5 with the G551D or other gating mutations in the United States, based on potential approval in March 2015
- Vertex expects that its combined non-GAAP R&D and SG&A expenses in 2015 will be in the range of $1.05 to $1.1 billion. The increase as compared to 2014 is primarily a result of launch preparation activities for lumacaftor in combination with ivacaftor and the planned pivotal Phase 3 development program for VX-661 in combination with ivacaftor. Vertex's expected non-GAAP R&D and SG&A expenses exclude stock-based compensation expense and certain other expenses recorded in 2015.

INDICATION AND IMPORTANT SAFETY INFORMATION FOR KALYDECO® (ivacaftor)

Ivacaftor (150 mg tablets) is a cystic fibrosis transmembrane conductance regulatory (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a *G551D* mutation in the *CFTR* gene.

In the United States (U.S.) and Europe, ivacaftor is also indicated for the treatment of CF in patients age 6 and older who have one of the following mutations in the *CFTR* gene: *G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R*. In Canada, ivacaftor is indicated for these same mutations and additionally for *G970R*. Additionally, in the U.S. ivacaftor is indicated for the treatment of CF in patients age 6 and older who have an *R117H* mutation in the *CFTR* gene.

Ivacaftor is not effective in patients with CF with 2 copies of the *F508del* mutation (*F508del/F508del*) in the *CFTR* gene. The safety and efficacy of ivacaftor in children with CF younger than 6 years of age have not been established.

Elevated liver enzymes (transaminases; ALT and AST) have been reported in patients receiving ivacaftor. It is recommended that ALT and AST be assessed prior to initiating ivacaftor, every 3 months during the first year of treatment, and annually thereafter. Patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the upper limit of normal. Following resolution of transaminase elevations, consider the benefits and risks of resuming ivacaftor dosing.

Use of ivacaftor with medicines that are strong CYP3A inducers, such as the antibiotics rifampin and rifabutin; seizure medications (phenobarbital, carbamazepine, or phenytoin); and the herbal supplement St. John's Wort, substantially decreases exposure of ivacaftor and may diminish effectiveness. Therefore, co-administration is not recommended. The dose of ivacaftor must be adjusted when used concomitantly with strong and moderate CYP3A inhibitors or when used in patients with moderate or severe hepatic disease.

Cases of non-congenital lens opacities/cataracts have been reported in pediatric patients up to 12 years of age treated with ivacaftor. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating ivacaftor treatment.

Ivacaftor can cause serious adverse reactions including abdominal pain and high liver enzymes in the blood. The most common side effects associated with ivacaftor include headache; upper respiratory tract infection (the common cold), including sore throat, nasal or sinus congestion, and runny nose; stomach (abdominal) pain; diarrhea; rash; and dizziness. These are not all the possible side effects of ivacaftor. A list of the adverse reactions can be found in the product labeling for each country where ivacaftor is approved. Patients should tell their healthcare providers about any side effect that bothers them or does not go away.

Please see KALYDECO (ivacaftor) U.S. Prescribing Information, EU Summary of Product Characteristics, Canadian Product Monograph, Australian Consumer Medicine Information and Product Information, Swiss Prescribing Information and Patient Information, and the New Zealand Datasheet and Consumer Medicine Information.

About Cystic Fibrosis

Cystic fibrosis is a rare, life-threatening genetic disease affecting approximately 75,000 people in North America, Europe and Australia. Today, the median predicted age of survival for a person with CF is between 34 and 47 years, but the median age of death remains in the mid-20s.

CF is caused by a defective or missing CFTR protein resulting from mutations in the *CFTR* gene. Children must inherit two defective *CFTR* genes — one from each parent — to have CF. There are more than 1,900 known mutations in the *CFTR* gene. Some of these mutations, which can be determined by a genetic, or genotyping test, lead to CF by creating non-working or too few CFTR proteins at the cell surface. The defective or missing CFTR protein results in poor flow of salt and water into and out of the cell in a number of organs, including the lungs. This leads to the buildup of abnormally thick, sticky mucus that can cause chronic lung infections and progressive lung damage.

About Vertex

Vertex is a global biotechnology company that aims to discover, develop and commercialize innovative medicines so people with serious diseases can lead better lives. In addition to our clinical development programs focused on cystic fibrosis, Vertex has more than a dozen ongoing research programs aimed at other serious and life-threatening diseases.

Founded in 1989 in Cambridge, Mass., Vertex today has research and development sites and commercial offices in the United States, Europe, Canada and Australia. For five years in a row, *Science* magazine has named Vertex one of its Top Employers in the life sciences. For additional information and the latest updates from the company, please visit www.vrtx.com.

Special Note Regarding Forward-looking Statements

This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, including, without limitation, Dr. Leiden's statements in the second paragraph of the press release, the information provided in the section captioned "Financial" and statements regarding (i) 2015 KALYDECO net revenue guidance; (ii) the expected timing and clinical trial designs for the pivotal Phase 3 program of VX-661 in combination with ivacaftor and the other planned studies described in this press release; (iii) the company's expectations regarding the number of people who may be eligible for KALYDECO by the end of 2015; (iv) the company's expectations regarding potential approvals for lumacaftor in combination with ivacaftor and additional approvals for ivacaftor; (v) the target date for the FDA to review the NDA for lumacaftor in combination with ivacaftor under PDUFA; (vi) the company's expectations regarding reimbursement discussions; (vii) Vertex's plans to initiate new studies, including the pivotal Phase 3 program of VX-661 in combination with ivacaftor and the study to evaluate lumacaftor in combination with ivacaftor in children 6 to 11; (viii) the company's expectations regarding next-generation correctors; and (ix) the company's research and early-stage development programs. While Vertex believes the forward-looking statements contained in this press release are accurate, there are a number of factors that could cause actual events or results to differ materially from those indicated by such forward-looking statements. Those risks and uncertainties include, among other things, that the company's expectations regarding its 2015 revenues and expenses may be incorrect (including because one or more of the company's assumptions underlying its expectations may not be realized), that regulatory authorities may not approve, or approve on a timely basis, lumacaftor in combination with ivacaftor, that data from the company's development programs may not support registration or further development of its compounds due to safety, efficacy or other reasons, and other risks listed under Risk Factors in Vertex's annual report and quarterly reports filed with the Securities and Exchange

Commission and available through the company's website at www.vrtx.com. Vertex disclaims any obligation to update the information contained in this press release as new information becomes available.

Webcast Information

The company will webcast its corporate presentation at the 33rd Annual J.P. Morgan Healthcare Conference on Monday, January 12 at 9:30 a.m. PT (12:30 p.m. ET). The audio portion of management's remarks can be accessed live through Vertex's website at www.vrtx.com in the "Investors" section under the "Events and Presentations" page.

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