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Vertex Announces Results of Phase 3 Study of Ivacaftor in People with CF who have the R117H Mutation

-Mean absolute treatment difference in lung function across all patients was 2.1 percentage points (p=0.20) and mean relative treatment difference was 5.0% (p=0.06)(n=69); study did not meet its primary endpoint-

-Pre-specified analysis of patients 18 years of age and older (n=50) showed statistically significant mean absolute treatment difference of 5.0 percentage points (p=0.01); mean relative treatment difference was 9.1% (p=0.008)-

-Vertex plans to meet with U.S. FDA in early 2014 to discuss these data and the potential submission of a supplemental New Drug Application in people with CF who have the R117H mutation-

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced data from a Phase 3 study of ivacaftor in 69 people 6 years of age and older with cystic fibrosis (CF) who have the R117H mutation. In the study, the mean absolute treatment difference in the change from baseline in percent predicted FEV_1 between treatment with ivacaftor and placebo was 2.1 percentage points (p=0.20) and the mean relative treatment difference in percent predicted FEV_1 was 5.0 percent (p = 0.06) through the 24-week treatment period among all patients (intent-to-treat analysis). The study did not meet its primary endpoint of the absolute change from baseline in FEV_1 (percent predicted forced expiratory volume in one second, FEV_1) throughout the treatment period for ivacaftor compared to placebo across all patients. A pre-specified subset analysis in patients 18 years of age and older (n=50) showed statistically significant improvements in lung function and other key secondary endpoints. In these patients, the mean absolute treatment difference in percent predicted FEV_1 between treatment with ivacaftor and placebo was 5.0 percentage points (p=0.01) and the mean relative treatment difference in percent predicted FEV_1 was 9.1 percent (p=0.008) through the 24-week treatment period. Vertex believes that the results show a clinical benefit for patients age 18 and older with the R117H mutation. The company plans to meet with the U.S. Food and Drug Administration (FDA) in early 2014 to discuss these data and the potential submission of a supplemental New Drug Application (sNDA) for people with the R117H mutation.

R117H is the most common residual function mutation. In North America, Europe and Australia, approximately 1,100 people with CF ages 6 and older have at least one copy of an R117H mutation. In the United States, approximately 300 people have the R117H mutation and are 18 years of age or older.

"With each study of ivacaftor, we continue to learn more about this disease and the effect of ivacaftor in patients with different CF mutations, ages and severity of disease," said Robert Kauffman, M.D., Ph.D., Senior Vice President and Chief Medical Officer at Vertex. "People with the R117H mutation exhibit a wide range of severity in their CF lung disease, but as patients get older, the disease often results in decreased lung function. While we are disappointed that the study in people with the R117H mutation did not meet its primary endpoint, we are encouraged by the significant improvements in lung function and other measures of CF observed in the subset of patients ages 18 and older who had established lung disease. We look forward to meeting with the FDA early next year to discuss these data with the goal of bringing ivacaftor to additional people with CF who may benefit from treatment."

About the Phase 3 Study in People with the R117H Mutation

The 24-week Phase 3 randomized double-blind study of ivacaftor enrolled 69 people with CF ages 6 and older who have at least one R117H mutation. Patients 12 years and older had FEV_1 at screening of 40 to 90 percent predicted and children ages 6 to 11 years of age had FEV_1 at screening of 40 to 105 percent predicted. The primary endpoint of the study was the absolute change from baseline in FEV_1 throughout the treatment period for ivacaftor compared to placebo across all patients (intent-to-treat).

Lung Function (FEV_1) Results In the Total Study Population: In the study, the mean absolute treatment difference in percent predicted FEV_1 between those treated with ivacaftor and placebo was 2.1 percentage points (p=0.20) and the mean relative

treatment difference in percent predicted FEV_1 was 5.0 percent (p = 0.06) through the 24-week treatment period. The treatment difference for this endpoint was not statistically significant, thus the study did not meet its primary endpoint. The mean absolute and relative percent predicted FEV_1 improvements during ivacaftor treatment (within-group) were 2.6 percentage points (p = 0.03) and 4.8 percent (p=0.01), respectively.

Secondary Endpoints: In the study, treatment with ivacaftor, regardless of age, resulted in statistically significant decreases in sweat chloride and improvement in patient-reported outcomes as measured by the respiratory domain of the Cystic Fibrosis Questionnaire Revised (CFQ-R). No significant differences in the frequency of pulmonary exacerbations or changes in body mass index were noted.

Additional Analyses: A subgroup analysis was conducted to evaluate the effect of ivacaftor on patients ages 18 and older and in patients ages 12 to 17 and 6 to 11. Data from this subgroup analysis are provided below:

- ***Patients Ages 18 and Older:*** 50 patients ages 18 years of age and older were enrolled in the study and had a mean baseline FEV_1 of 65 percent. In these patients, a pre-specified subgroup analysis showed a statistically significant mean absolute treatment difference of 5.0 percentage points (p=0.01). This corresponded to a mean relative treatment difference of 9.1 percent (p=0.008). An additional analysis was also conducted on FEV_1 4 weeks following the completion of treatment with ivacaftor. Mean lung function returned toward baseline in the patients who received ivacaftor, who showed a -3.1 percentage point (p=0.001) mean absolute within-group change from Week 24 to Week 28 (4 weeks after the end of treatment). Data on patients 18 and older are provided below:

Subgroup Analysis — FEV_1 and Other Measures in Patients 18 and Older

	Ivacaftor (n=24)	Placebo (n=26)	Treatment Difference
Mean Absolute Change in FEV_1*	4.5 (p=0.002)	-0.5 (p=0.728)	5.0 (p=0.01)
Mean Relative Change in FEV_1	7.7 (p=0.002)	-1.5 (p=0.526)	9.1 (p=0.008)
Proportion of Patients with Mean Absolute Improvement in FEV_1 of 5 percentage points or more	54.2%	15.4%	38.8% (p=0.007)
CFQ-R Score (respiratory domain)*	12.2 (p= < 0.0001)	-0.5 (p=0.861)	12.6 (p=0.002)
*Pre-specified analyses			

In the patients ages 18 and older, statistically significant changes in secondary endpoints, including patient-reported outcomes as measured by the respiratory domain of the Cystic Fibrosis Questionnaire Revised (CFQ-R) and sweat chloride, were observed. No significant differences in the frequency of pulmonary exacerbations or changes in body mass index were noted.

- ***Patients Ages 12 to 17:*** Two patients ages 12 to 17 enrolled in the study; one received placebo and one received ivacaftor. There were too few patients to make a statistical comparison in this age range.
- ***Patients Ages 6 to 11:*** Seventeen patients ages 6 to 11 were enrolled in the study and had a mean baseline FEV_1 of 96 percent. In these patients, there was a mean absolute decline from baseline in FEV_1 of -2.8 percentage points (p=0.132) in patients who received ivacaftor (n=9) compared to a mean absolute increase from baseline in FEV_1 of 3.5 percentage points (p=0.084) for those who received placebo (n=8). The mean absolute treatment difference was -6.3 percentage points (p=0.03).

Safety Results In the Total Study Population: The safety and tolerability results observed in this study were consistent with those observed in prior Phase 3 studies of ivacaftor monotherapy in people with CF who have the G551D or other gating mutations. The most commonly observed adverse events in those who received ivacaftor were infective pulmonary exacerbation, cough and headache, which occurred with similar frequency compared to those who received placebo. Serious adverse events occurred in 17 percent of patients who received placebo versus 12 percent for patients who received ivacaftor.

Additional Studies to Potentially Expand Number of People Eligible for Ivacaftor

In addition to the study in people with CF who have the R117H mutation announced today, multiple additional studies are ongoing or complete that are designed to evaluate whether additional people with CF may benefit from treatment with ivacaftor. Vertex today provided the following updates on its recent regulatory submissions for people ages 6 and older with gating mutations and on other ongoing studies of ivacaftor:

- **Gating Mutations Study:** Vertex today announced that the U.S. FDA accepted its sNDA for ivacaftor and granted

Vertex's request for six-month Priority Review. A target review date of March 27, 2014 was set under the Prescription Drug User Fee Act (PDUFA) for the FDA's approval decision. Approximately 400 people ages 6 and older have non-G551D gating mutations in North America, Australia and Europe.

- **Study in Children Ages 2 to 5 with Gating Mutations:** A Phase 3 study of ivacaftor in children with CF ages 2 to 5 who have a gating mutation is ongoing and fully enrolled. Data from this study are expected in the second quarter of 2014 to support a potential NDA submission in the second half of 2014. In North America, Europe and Australia, approximately 300 children ages 2 to 5 have a gating mutation.
- **Residual Function Study:** Enrollment is complete in a Phase 2 proof-of-concept study evaluating ivacaftor in people ages 12 and older with CF who have clinical evidence of residual CFTR function. Data from this study are expected in the second quarter of 2014. In North America, Europe and Australia, more than 3,000 people ages 6 and older have non-R117H *CFTR* mutations that result in residual function.

About KALYDECO™ (ivacaftor)

KALYDECO is the first medicine to treat the underlying cause of CF in people with the G551D mutation in the CFTR gene. Known as a CFTR potentiator, KALYDECO is an oral medicine that aims to help the CFTR protein function more normally once it reaches the cell surface, to help hydrate and clear mucus from the airways. KALYDECO (150mg, q12h) was first approved by the U.S. Food and Drug Administration in January 2012, by the European Medicines Agency in July 2012, by Health Canada in November 2012, by the Therapeutic Goods Administration in Australia in July 2013 and by MedSafe in New Zealand in December 2013 for use in people with CF ages 6 and older who have at least one copy of the G551D mutation in the *CFTR* gene.

Vertex retains worldwide rights to develop and commercialize KALYDECO.

INDICATION AND IMPORTANT SAFETY INFORMATION FOR KALYDECO™ (ivacaftor)

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

Ivacaftor is not for use in people with CF due to other mutations in the CFTR gene. It is not effective in patients with CF with 2 copies of the *F508del* mutation (*F508del/F508del*) in the *CFTR* gene. The efficacy and safety of ivacaftor in children younger than 6 years of age have not been evaluated.

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 which may diminish effectiveness. Therefore, co-administration is not recommended.

The dose of ivacaftor must be adjusted when used concomitantly with potent and moderate CYP3A inhibitors. The dose of ivacaftor must be adjusted when used in patients with moderate or severe hepatic disease.

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 full U.S. Prescribing Information for KALYDECO at www.KALYDECO.com, the EU Summary of Product Characteristics for KALYDECO at http://goo.gl/N3Tz4, the Canadian Product Monograph for KALYDECO at www.vrtx.ca and the Australian Consumer Medical Information and Product Information for KALYDECO (ivacaftor) at http://bit.ly/18wlMld.

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 1,800 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 protein at the cell surface. The absence of working 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.

Collaborative History with Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT)

Vertex initiated its CF research program in 1998 as part of a collaboration with CFFT, the nonprofit drug discovery and development affiliate of the Cystic Fibrosis Foundation. This collaboration was expanded to support the accelerated discovery and development of Vertex's CFTR modulators.

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. Vertex scientists and our collaborators are working on new medicines to cure or significantly advance the treatment of cystic fibrosis, hepatitis C, rheumatoid arthritis and other life-threatening diseases. In addition to our clinical development programs, Vertex has more than a dozen ongoing preclinical 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 four 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. Kauffman's statements in the third paragraph of this press release and statements regarding (i) Vertex's plan to meet with the FDA in early 2014 and discuss the study data and potential sNDA submission, (ii) Vertex's belief that the study data show a clinical benefit for patients age 18 and older with the R117H mutation, and (iii) Vertex's ongoing studies evaluating ivacaftor monotherapy, including its expectations regarding the timing of the receipt of data from these studies and potential timelines for regulatory submissions and approval decisions. 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 differmaterially from those indicated by such forward-looking statements. Those risks and uncertainties include, among other things, that results from the Phase 3 study of ivacaftor in people with CF who have the R117H mutation may not support an sNDA submission, studies of ivacaftor monotherapy may be delayed or prevented, the outcomes of Vertex's ongoing clinical studies may be delayed or 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.

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