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Vertex Announces Data from 12-Week Phase 2 Safety Study of VX-661 in Combination with Ivacaftor in People with Cystic Fibrosis Who Have Two Copies of the F508del Mutation

-The combination was generally well tolerated and all patients completed 12 weeks of treatment-

-Mean within-group absolute improvement from baseline in lung function of 4.4 (p=0.009) and 3.0 (p=0.026) percentage points at week 4 and through 12 weeks of treatment, respectively, in patients who received VX-661 (100 mg once daily) in combination with ivacaftor (150 mg every 12 hours)-

-Data were consistent with prior Phase 2 studies of VX-661 and ivacaftor and support ongoing Phase 3 program evaluating VX-661 in combination with ivacaftor in people with one or two copies of the F508del mutation-

BOSTON--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq:VRTX) today announced data from a 12-week Phase 2 study evaluating VX-661 in combination with ivacaftor in 39 people with CF ages 18 and older who have two copies of the F508del mutation. The study evaluated two doses of VX-661 (100 mg once daily or 50 mg every 12 hours) in combination with ivacaftor (150 mg every 12 hours). The primary endpoint of the study was safety. The study showed that the combination regimen was generally well tolerated, and all patients completed 12 weeks of treatment. The most common adverse events were pulmonary exacerbation, which occurred in 38 percent of all patients who received VX-661 and 44 percent of those who received placebo, and cough, which occurred in 33 percent of all patients who received VX-661 and 39 percent of those who received placebo.

Secondary endpoints evaluated the effect of the combination on lung function (percent predicted forced expiratory volume in one second; $ppFEV_1$), and the mean within-group absolute improvement from baseline in $ppFEV_1$ for those who received 100 mg of VX-661 in combination with ivacaftor (n=15) was 4.4 (p=0.009) and 3.0 (p=0.026) percentage points at week 4 and through 12 weeks of treatment, respectively. Consistent with prior Phase 2 studies that evaluated 4 weeks of treatment with VX-661 in combination with ivacaftor, this study showed a rapid improvement in lung function within four weeks of treatment, and after patients completed treatment, lung function returned to baseline.

These safety and efficacy data, together with other data from multiple previously completed Phase 2 studies of VX-661, support Vertex's ongoing Phase 3 program of VX-661 in combination with ivacaftor. The Phase 3 program is evaluating VX-661 (100 mg once daily) in combination with ivacaftor (150 mg every 12 hours) and consists of four Phase 3 studies, including a study in people with two copies of the F508del mutation that began enrollment in February. The other three studies will enroll people with CF who have one copy of the F508del mutation and a second mutation that is either a gating mutation, residual function mutation or a mutation that results in minimal CFTR function.

"The safety and efficacy data from this study are consistent with prior Phase 2 studies of VX-661 in combination with ivacaftor and provide further support for our ongoing Phase 3 program in people with one or two copies of the F508del mutation," said Jeffrey Chodakewitz, M.D., Executive Vice President and Chief Medical Officer at Vertex.

Cystic fibrosis is caused by a defective or missing CFTR protein resulting from mutations in the *CFTR* gene. In people with two copies of the most common mutation in the *CFTR* gene, F508del, little to no CFTR protein reaches the cell surface. VX-661, known as a CFTR corrector, is designed to address the processing defect of F508del-CFTR to enable it to reach the cell surface. Ivacaftor, known as a CFTR potentiator, keeps cell surface CFTR protein channels open more often to increase the flow of salt and water.

About the Study

The Phase 2 randomized, double-blind, placebo-controlled study treated 39 people with CF ages 18 and older with two copies of the F508del mutation. Fifteen patients received VX-661 (100 mg once daily) in combination with ivacaftor (150 mg every 12 hours) and 18 patients received placebo. The study also enrolled six patients in an arm that evaluated VX-661 (50 mg every 12 hours) in combination with ivacaftor (150 mg every 12 hours) that was included in the study prior to selection of the 100 mg VX-661 once daily dose to be used for further development. The mean $ppFEV_1$ at baseline was 57.2 percentage points and the mean baseline sweat chloride was 106.2 mmol/L. The baseline characteristics were well balanced across treatment arms. The

primary endpoint of the study was safety, and secondary endpoints evaluated the effect of the combination on $ppFEV_1$, sweat chloride and other measures.

Primary Endpoint: The combination of VX-661 and ivacaftor was generally well tolerated, and all patients completed 12 weeks of treatment. The majority of adverse events were mild to moderate in severity, and no patients discontinued treatment in the study due to adverse events. The most common adverse events were pulmonary exacerbation, which occurred in 38 percent of all patients who received VX-661 and 44 percent of those who received placebo, and cough, which occurred in 33 percent of all patients who received VX-661 and 39 percent of those who received placebo. Serious adverse events occurred in 24 percent of people who received the combination regimen and 39 percent of those who received placebo. The types and frequency of adverse events were generally similar between the treatment and placebo groups.

Secondary Endpoints: In the patients who received VX-661 (100 mg once daily) in combination with ivacaftor (150 mg every 12 hours), mean within-group absolute improvements from baseline in $ppFEV_1$ of 4.4 and 3.0 percentage points were observed at week 4 and through 12 weeks of treatment, respectively. The mean $ppFEV_1$ improvement observed through 12 weeks of treatment for those in the treatment group returned to baseline during the post-treatment washout period. The mean within-group absolute change in $ppFEV_1$ for those who received placebo was -0.4 and 1.0 percentage points at week 4 and through 12 weeks, respectively. Additional information on the mean within-group absolute changes from baseline in $ppFEV_1$ is provided below:

Mean Absolute Change from Baseline in $ppFEV_1$ (percentage points)		**VX-661 (100 mg once daily) + ivacaftor (150 mg every 12 hours) (n=15)**	**Placebo (n=18)**
At Week 4	**Within Group**	4.4 (*p=0.009)*	-0.4 *(p=0.827)*
Through Week 12	**Within Group**	3.0 (*p=0.026)*	1.0 *(p=0.451)*
28 Days Post-Treatment	**Within Group**	0.5	1.4

In addition, statistically significant mean within-group absolute decreases in sweat chloride were observed for the group who received VX-661 (100 mg once daily) in combination with ivacaftor. These changes were generally modest and consistent with results from a prior Phase 2 study of this dosing regimen in people with two copies of the F508del mutation.

In the six patients who received VX-661 (50 mg every 12 hours) in combination with ivacaftor, the mean within-group absolute improvements from baseline in $ppFEV_1$ observed at week 4 and through 12 weeks of treatment were 0.9 (p=0.741) and 0.6 (p=0.776) percentage points. The 28-day post-treatment change from baseline in $ppFEV_1$for this group was 1.1 percentage points. There was a statistically significant decrease in sweat chloride for this group that was generally modest.

Prior Studies of VX-661 and Ivacaftor in People with the F508del Mutation

Prior to this 12-week study, Vertex completed a 4-week Phase 2 study of VX-661 in combination with ivacaftor in people with two copies of the F508del mutation. A subsequent study evaluated the combination regimen in people with both the F508del mutation and G551D mutation who were already taking KALYDECO. Data from these studies were reported previously. Across these studies, the safety profile for the combination treatment regimens was similar. In the study that enrolled people with two copies of the F508del mutation, the mean within-group absolute changes from baseline in $ppFEV_1$ for the two highest doses are noted below:

Mean Absolute Change from Baseline in $ppFEV_1$ (percentage points)		**VX-661 (100 mg once daily) + ivacaftor (150 mg q12h) (n=15)**	**VX-661 (150 mg once daily) + ivacaftor (150 mg q12h) (n=16)**	**Placebo (n=23)**
At Week 4	**Within Group**	4.4 (p=0.0019)	4.1 (p=0.0031)	-0.4 (p=0.757)
28 Days Post-Treatment	**Within Group**	0.5	0.7	0.6

In the study that enrolled people with both the F508del mutation and G551D mutation who were already taking KALYDECO (ivacaftor), the mean within-group absolute changes from baseline in $ppFEV_1$ were 4.6 percentage points (p=0.012) through week 4 and 1.6 percentage points 28 days after the end of treatment.

Based on Phase 2 data generated to date, Vertex is currently conducting a broad Phase 3 development program evaluating

the combination of VX-661 (100 mg once daily) in combination with ivacaftor (150 mg every 12 hours) in people with one or two copies of the F508del mutation. The designs of these studies were provided in January 2015, and a summary of the Phase 3 program is provided below:

- **Two Copies of the F508del Mutation:** Enrollment is ongoing in a Phase 3 study evaluating 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 is absolute change in $ppFEV_1$ through six months of treatment versus placebo. The study will enroll approximately 500 patients in North America and Europe.
- **One Copy of the F508del Mutation and a Second Mutation That Results in Residual CFTR Function:** In April, 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.
- **One Copy of the F508del Mutation and a Second Mutation that Results in a Gating Defect in the CFTR Protein:** In May, 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.
- **One Copy of the F508del Mutation and A Second Mutation That Results in Minimal CFTR Function:** In mid-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.

INDICATION AND IMPORTANT SAFETY INFORMATION FOR KALYDECO® (ivacaftor)

Ivacaftor is a cystic fibrosis transmembrane conductance regulatory (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF). In the U.S. (in patients age 2 years and older) and Europe (in patients age 6 years and older), ivacaftor is indicated for patients who have one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R. In Canada (in patients 6 years and older), ivacaftor is indicated for patients with these same mutations and also for patients with the G970R mutation. Additionally, in the U.S. (in patients age 2 years and older) and Canada (in patients age 18 years and older) ivacaftor is indicated for the treatment of CF in patients who have an R117H mutation in the CFTR gene.

Ivacaftor is available as 150 mg tablets in countries where it is approved for patients age 6 years and older, and additionally in the U.S. as 50 mg and 75 mg oral granules for patients age 2 to less than 6 years.

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 2 years of age have not been studied. The use of ivacaftor in children under the age of 2 years is not recommended.

High liver enzymes (transaminases; ALT and AST) have been reported in patients with CF receiving ivacaftor. Transaminase elevations were more common in patients with a history of transaminase elevations or in patients who had abnormal transaminases at baseline. 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. For patients with a history of transaminase elevations, more frequent monitoring of liver function tests should be considered. 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 treated with ivacaftor. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating ivacaftor treatment.

Serious adverse reactions that occurred more frequently with ivacaftor included abdominal pain, increased liver enzymes, and low blood sugar (hypoglycemia). The most common side effects associated with ivacaftor include headache; upper respiratory tract infection (common cold), including sore throat, nasal or sinus congestion, and runny nose; stomach (abdominal) pain; diarrhea; rash; nausea; 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 protein at the cell surface. The defective function or absence of CFTR proteins in people with CF results in poor flow of salt and water into and out of the cell in a number of organs. In 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. 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. Chodakewitz's statements in the fourth paragraph of the press release, and the information with respect to the timing and plans for Phase 3 development of VX-661 in combination with ivacaftor. While Vertex believes the forward-looking statements contained in this press release are accurate, these forward-looking statements represent the company's beliefs only as of the date of this press release and 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 Vertex could experience unforeseen delays in the development of VX-661 in combination with ivacaftor 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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