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Vertex Initiates Phase 3 Study of VX-659, Tezacaftor and Ivacaftor as a Triple Combination Regimen for People with Cystic Fibrosis Who Have Two Copies of the F508del Mutation

-Global Phase 3 study to enroll approximately 100 patients with the most common genetic form of the disease-

-Phase 2 data showed mean absolute improvement in ppFEV$_1$ of 9.7 percentage points when VX-659 was added in people with CF who have two F508del mutations who were already receiving tezacaftor and ivacaftor; triple combination regimen was generally well tolerated-

BOSTON--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced that it is initiating a Phase 3 study of VX-659, tezacaftor and ivacaftor as an investigational triple combination regimen for people with cystic fibrosis (CF) who have two copies of the *F508del* mutation, the most common genetic form of the disease. The study will enroll approximately 100 patients, and the primary endpoint of the study is the mean absolute change from baseline in percent predicted forced expiratory volume in one second (ppFEV$_1$) at week four of treatment. The study is designed to support the submission of an application for approval in patients with two copies of the *F508del* mutation in the U.S. using data from the 4-week primary efficacy endpoint together with 24-week safety data generated from the recently initiated Phase 3 study in patients with one *F508del* mutation and one minimal function mutation.

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The initiation of the Phase 3 study in people with CF who have two copies of the *F508del* mutation is based on data announced today from a Phase 2 study that showed a mean absolute improvement in ppFEV$_1$ of 9.7 percentage points from baseline through week four of treatment when VX-659 (400 mg) was added in people with CF who have two *F508del* mutations and were already receiving tezacaftor in combination with ivacaftor. In the Phase 2 study, the VX-659 triple combination regimen was generally well tolerated, the majority of adverse events were mild to moderate in severity and there were no discontinuations due to adverse events.

"We continue to make rapid and significant progress in our efforts to advance our two triple combination regimens into Phase 3 development, with an ultimate goal of bringing the best triple combination to patients as quickly as possible," said Jeffrey Chodakewitz, M.D., Executive Vice President and Chief Medical Officer at Vertex. "The first Phase 3 study we announced in February is designed to support approval of the VX-659 triple combination in patients with one *F508del* mutation and one minimal function mutation who currently have no treatment that addresses the underlying cause of disease. This second study is designed to enable us to broaden the potential label for this regimen to include those with the most common genetic form of cystic fibrosis."

About the Phase 3 Study

The randomized, double-blind, controlled Phase 3 study will evaluate four weeks of treatment with VX-659 or placebo in combination with tezacaftor and ivacaftor in approximately 100 patients ages 12 years or older who have two *F508del* mutations. Approximately 50 patients will receive VX-659, tezacaftor and ivacaftor and approximately 50 will receive placebo, tezacaftor and ivacaftor. All patients will receive tezacaftor in combination with ivacaftor during a 4-week run-in prior to the start of the triple combination treatment period. The primary endpoint of the study is the mean absolute change in lung function (ppFEV$_1$) from baseline (end of the 4-week tezacaftor/ivacaftor run-in) at week four of treatment with VX-659 in combination with tezacaftor and ivacaftor compared to those who received placebo, tezacaftor and ivacaftor. Key secondary endpoints will also be measured at week four and include changes in patient-reported outcomes as measured by the respiratory domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) and change in sweat chloride.

The study will evaluate a fixed-dose combination of VX-659 (240 mg) with tezacaftor (100 mg) and ivacaftor (150 mg) in the morning followed by ivacaftor (150 mg) in the evening, which is the same dosing regimen being evaluated in the ongoing Phase 3 study in patients with one *F508del* mutation and one minimal function mutation. An open-label extension study will be conducted where all eligible patients, including those who received placebo, tezacaftor and ivacaftor, will receive the

triple combination regimen for up to an additional 96 weeks.

The study is designed to support an application for U.S. Food and Drug Administration (FDA) approval of the VX-659 triple combination regimen in patients with two copies of the *F508del* mutation based on data from the 4-week primary efficacy analysis and secondary safety analysis and on 24-week safety data from the Phase 3 study in patients with one *F508del* mutation and one minimal function mutation. Vertex plans to use the study in patients with two *F508del* mutations to broaden the potential label for the VX-659 triple combination regimen and does not anticipate that the study will impact its initial planned submission of a New Drug Application to the U.S. FDA for patients with one *F508del* mutation and one minimal function mutation. Data from the study in patients with two *F508del* mutations will also be used to support planned regulatory submissions in Europe and other regions.

Vertex plans to initiate multiple additional Phase 3 studies of VX-659 and VX-445 triple combination regimens in 2018. Regulatory discussions are ongoing regarding the design of these additional Phase 3 studies.

Phase 2 Data in Patients with Two *F508del* Mutations

The data announced today are from Part 2 of an ongoing randomized, double-blind, controlled Phase 2 study where the primary objectives are safety, tolerability and efficacy as assessed by mean absolute change in $ppFEV_1$ from baseline (end of the 4-week tezacaftor/ivacaftor run-in period) through week four of treatment. Secondary endpoints include absolute change in sweat chloride and change in the CFQ-R respiratory domain score, among others.

All patients received a 4-week run-in of tezacaftor in combination with ivacaftor. Patients were then randomized to add either VX-659 or placebo to tezacaftor and ivacaftor for four weeks. After the 4-week triple combination dosing period, all patients received four weeks of tezacaftor and ivacaftor, followed by a 4-week safety follow-up period. In the triple combination dosing period of the study, patients received a morning dose of VX-659 (400 mg), or placebo, in addition to a fixed-dose combination of tezacaftor (100 mg) and ivacaftor (150 mg) in the morning followed by an evening dose of ivacaftor (150 mg) alone.

Safety Data: The triple combination regimen was generally well tolerated. The majority of adverse events were mild or moderate. No serious adverse events were reported in the triple combination group and one serious adverse event (pulmonary exacerbation) was reported in the group that received tezacaftor in combination with ivacaftor. There were no discontinuations due to adverse events in either treatment group, and there were no treatment interruptions. The most common adverse events (> 10%), regardless of treatment group, were cough, infective pulmonary exacerbation, nasal congestion, nausea, sputum increased, vomiting, headache, abdominal pain upper, blood creatine phosphokinase increased, diarrhea, oropharyngeal pain, rash and upper respiratory tract infection.

Efficacy Data: This part of the study evaluated the addition of VX-659, or placebo, to ongoing tezacaftor/ivacaftor treatment for a 4-week triple combination dosing period in 29 patients who have two *F508del* mutations (11 in the placebo/tezacaftor/ivacaftor arm, 18 in VX-659 triple combination arm). A summary of the within-group lung function and sweat chloride data is provided below:

VX-659 Added to Ongoing Treatment with Tezacaftor and Ivacaftor in Patients with Two *F508del* Mutations

Mean Absolute Within-Group Change From Baseline Through Day 29*	**Mean Absolute Within-Group Change in $ppFEV_1$ (percentage points)**	**Mean Absolute Within-Group Change in Sweat Chloride (mmol/L)**
Placebo + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	0.0 (p=0.9926)	+3.0 (p=0.2977)
VX-659 (400mg QD) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+9.7 (p < 0.0001)	-42.2 (p < 0.0001)

** all p-values are within group p-values based on mixed effect models; values expressed as 'Through Day 29' are the average of Day 15 and Day 29 measures*

A secondary endpoint in the study measured mean absolute within-group change in the respiratory domain of CFQ-R,[1] a validated patient-reported outcome measure, at Day 29. The mean absolute improvement for patients who received the VX-659 triple combination was 19.5 points. The improvement for those who received placebo in addition to tezacaftor and ivacaftor was 2.9 points.

About CF

CF is a rare, life-shortening genetic disease affecting approximately 75,000 people in North America, Europe and Australia.

CF is caused by a defective or missing cystic fibrosis transmembrane conductance regulator (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 approximately 2,000 known mutations in the *CFTR* gene. Some of these mutations, which can be determined by a genetic test, or genotyping test, lead to CF by creating non-working or too few CFTR proteins at the cell surface. The defective function or absence of CFTR protein 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 in many patients that eventually leads to death. The median age of death is in the mid-to-late 20s.

About Vertex

Vertex is a global biotechnology company that invests in scientific innovation to create transformative medicines for people with serious and life-threatening diseases. In addition to clinical development programs in CF, Vertex has more than a dozen ongoing research programs focused on the underlying mechanisms of other serious diseases.

Founded in 1989 in Cambridge, Mass., Vertex's headquarters is now located in Boston's Innovation District. Today, the company has research and development sites and commercial offices in the United States, Europe, Canada and Australia. Vertex is consistently recognized as one of the industry's top places to work, including being named to *Science* magazine's Top Employers in the life sciences ranking for eight years in a row. For additional information and the latest updates from the company, please visit www.vrtx.com.

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

Vertex initiated its CF research program in 2000 as part of a collaboration with CFFT, the nonprofit drug discovery and development affiliate of the Cystic Fibrosis Foundation. KALYDECO® (ivacaftor), ORKAMBI® (lumacaftor/ivacaftor), SYMDEKO™ (tezacaftor/ivacaftor and ivacaftor), VX-440, VX-152, VX-659 and VX-445 were discovered by Vertex as part of this collaboration.

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 third paragraph and the information provided regarding (i) the timing and design of Vertex's Phase 3 study for VX-659, (ii) the potential to use the study to support regulatory applications, (iii) the relationship between the study in patients with two copies of the *F508del* mutation and the study that the company is conducting in patients with one *F508del* mutation and one minimal function mutation and (iv) Vertex's plans to initiate multiple additional Phase 3 studies of VX-659 and VX-445 triple combination regimens in 2018. 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: (i) that Vertex could experience unforeseen delays in initiating its Phase 3 studies to evaluate VX-659 and/or VX-445, (ii) that data from the Phase 3 development programs may not support approval of the company's triple combination regimens due to safety, efficacy or other reasons, and (iii) 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.

(VRTX-GEN)

[1] CFQ-R results reported are based on a mixed effect model not adjusted for baseline CFQ-R

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