Vertex Selects Triple Combination Regimen of VX-445, Tezacaftor and Ivacaftor to Submit for Global Regulatory Approvals in Cystic Fibrosis

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-Mean absolute improvement in ppFEV$_1$ of 14.3 percentage points from baseline through week 24 of treatment compared to placebo (p<0.0001) in patients with one F508del mutation and one minimal function mutation-

-Statistically significant improvements observed in all key secondary endpoints in patients with one F508del mutation and one minimal function mutation, including a 63% reduction in the annualized rate of pulmonary exacerbations compared to placebo (p<0.0001)-

-Submission of a New Drug Application in the U.S. planned for the third quarter of 2019 followed by a Marketing Authorization Application in the EU in the fourth quarter of 2019-

BOSTON--(BUSINESS WIRE)--May 30, 2019-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced that it has selected the triple combination of the next-generation corrector VX-445 (elexacaftor), tezacaftor and ivacaftor to submit for potential global regulatory approvals for people ages 12 and older with cystic fibrosis (CF). Final data announced today from a 24-week Phase 3 study in people with one *F508del* mutation and one minimal function mutation and from a 4-week Phase 3 study in people with two *F508del* mutations will form the basis of these submissions. Vertex previously announced that both of these Phase 3 studies met their primary endpoints, and the company today announced the final results of these studies, including results for key secondary endpoints and safety data.

In each study, treatment with the VX-445 triple combination regimen resulted in statistically significant improvements in all key secondary endpoints. Data from the 24-week study in people with one *F508del* mutation and one minimal function mutation showed a mean absolute improvement in percent predicted forced expiratory volume in one second (ppFEV$_1$) of 14.3 percentage points from baseline (p<0.0001) and a 63% reduction in the annualized rate of pulmonary exacerbations (p<0.0001) through week 24 in patients who received the VX-445 triple combination regimen compared to those who received triple placebo. The VX-445 triple combination regimen was generally well tolerated across the two Phase 3 studies. In the study in people with one *F508del* mutation and one minimal function mutation, 2 and 0 patients, respectively, who received the VX-445 triple combination or triple placebo discontinued treatment due to adverse events. There were no discontinuations for adverse events in either arm of the study in people with two *F508del* mutations.

Vertex plans to submit a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) in the third quarter of 2019 and a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) in the fourth quarter of 2019 based on these data in people with CF ages 12 years and older who have one *F508del* mutation and one minimal function mutation and in people with two *F508del* mutations.

“The substantial improvements in lung function and other measures of CF seen in these Phase 3 studies are unprecedented and represent a defining moment in the journey to provide medicines that treat the underlying cause of CF to the vast majority of people with CF,” said Steven M. Rowe, M.D., M.S.P.H., Director of the Gregory Fleming James Cystic Fibrosis Research Center, University of Alabama at Birmingham and co-chair of Vertex's Triple Combination Steering Committee.

“People with CF who have one *F508del* mutation and one minimal function mutation are the largest remaining group of CF patients without a treatment option for the underlying cause of their disease. The final Phase 3 data announced today represent a significant step toward bringing a disease modifying medicine to these patients, as well as toward providing significantly enhanced benefits to patients with two *F508del* mutations,” said Reshma Kewalramani, M.D., Executive Vice President, Global Medicines Development and Medical Affairs and Chief Medical Officer at Vertex. “We could not have achieved this important milestone without the support of the entire CF community, and we are particularly grateful to those who participated in the triple combination clinical trials. We now look forward to completing our regulatory submissions with the aim of bringing the VX-445 triple combination regimen to as many patients as possible.”

Vertex conducted two Phase 3 programs in parallel that evaluated two different triple combination regimens with the goal of selecting the best regimen to submit for global regulatory approvals. One program evaluated VX-659 in combination with tezacaftor and ivacaftor, and the other program evaluated VX-445 in combination with tezacaftor and ivacaftor. Each of the programs consisted of a Phase 3 study in people with one *F508del* mutation and one minimal function mutation and a Phase 3 study in people with two *F508del* mutations. The Phase 3 studies in both programs met their primary endpoints and showed statistically significant improvements across all key secondary endpoints. Additionally, each of the two triple combination regimens was generally well tolerated, and more than 98% of patients in each of the two programs completed the Phase 3 study treatment periods and elected to enroll in the open-label extension study for each regimen.

Both regimens showed highly similar and positive benefit-risk profiles. Vertex ultimately determined that the VX-445 triple combination regimen could benefit the greatest number of CF patients. This decision was based on a detailed assessment of multiple factors, including favorable profiles for safety, tolerability and drug-drug interactions, the ability for co-administration with hormonal contraceptives, and the lack of photosensitivity.

About the Phase 3 Study of VX-445, Tezacaftor and Ivacaftor in People with One *F508del* Mutation and One Minimal Function Mutation

The final 24-week efficacy and safety data announced today are from a randomized, double-blind, placebo-controlled Phase 3 study that enrolled people ages 12 and older with one *F508del* mutation and one minimal function mutation. Patients randomized to the triple combination arm received a fixed-dose combination of VX-445 (200 mg), tezacaftor (100 mg) and ivacaftor (150 mg) in the morning followed by ivacaftor (150 mg) in the evening. Patients randomized to the control arm received triple placebo in the morning and ivacaftor placebo in the evening.

The study randomized and dosed 403 patients, including 200 in the VX-445 triple combination regimen arm and 203 in the placebo arm. 400 patients completed the 24-week treatment period, including 197 in the VX-445 triple combination regimen arm and 203 in the placebo arm. All 400 patients

elected to enroll in the 96-week open-label extension study where all patients receive the VX-445 triple combination regimen.

Efficacy Results: As previously announced, treatment with the VX-445 triple combination regimen resulted in a mean absolute improvement in $ppFEV_1$ of 13.8 percentage points from baseline at week 4 compared to triple placebo ($p<0.0001$), which was the primary endpoint of the study in the U.S. This improvement in $ppFEV_1$ was maintained through 24 weeks of treatment in the study, as announced today. In addition, statistically significant improvements in all key secondary endpoints were observed after treatment with the VX-445 triple combination. A summary of the Phase 3 efficacy data, including results announced today for 24-week key secondary endpoints, is provided below:

		Triple Placebo (N=203)	VX-445/TEZ/IVA (N=200)	Treatment Difference*
Primary Endpoint**				
Absolute Change in $ppFEV_1$ from Baseline at Week 4		-0.2	13.6	13.8 (p<0.0001)
24-Week Key Secondary Endpoints**				
Absolute Change in $ppFEV_1$ from Baseline Through Week 24		-0.4	13.9	14.3 (p<0.0001)
Number of Pulmonary Exacerbations Through Week 24	Number of Events (rate per 48 weeks)	113 (0.98)	41 (0.37)	---
	Rate Ratio	---	---	0.37 (p<0.0001)
Absolute Change in Sweat Chloride from Baseline Through Week 24		-0.4	-42.2	-41.8 (p<0.0001)
Absolute Change in CFQ-R Respiratory Domain from Baseline Through Week 24		-2.7	17.5	20.2 (p<0.0001)
Absolute Change in BMI from Baseline at Week 24		0.09	1.13	1.04 (p<0.0001)

**Treatment difference provided as the outcome measure for changes in $ppFEV_1$, sweat chloride, CFQ-R and BMI; Rate ratio provided as the outcome measure for the number of pulmonary exacerbations*

***The primary endpoint was evaluated as part of a previously announced interim analysis; secondary endpoints were evaluated as part of the final analysis; Absolute change in $ppFEV_1$ from baseline through week 24 was the primary endpoint of the study in the EU*

Safety Results: The VX-445 triple combination was generally well tolerated in this 24-week study. The majority of adverse events were mild or moderate. Serious adverse events were observed in 13.9% (n=28) of patients who received the VX-445 triple combination regimen and in 20.9% (n=42) of patients who received triple placebo. The most common adverse events that occurred in 15% or more of patients, regardless of treatment arm, were infective pulmonary exacerbation, sputum increased, headache and cough. Two patients (1%) who received the VX-445 triple combination discontinued treatment due to adverse events, and 0 (0%) patients who received triple placebo discontinued treatment due to adverse events.

About the Phase 3 Study of VX-445, Tezacaftor and Ivacaftor in People with Two *F508del* Mutations

The final 4-week data announced today are from a randomized, double-blind, controlled Phase 3 study that enrolled people ages 12 and older with two *F508del* mutations. All patients received tezacaftor in combination with ivacaftor during a 4-week run-in prior to randomization. Patients randomized to the active treatment arm received a fixed-dose combination of VX-445 (200 mg), tezacaftor (100 mg) and ivacaftor (150 mg) in the morning followed by ivacaftor (150 mg) in the evening. Patients randomized to the control arm received placebo, tezacaftor (100 mg) and ivacaftor (150 mg) in the morning followed by ivacaftor (150 mg) in the evening.

The study randomized and dosed 107 patients, including 55 in the VX-445 triple combination regimen arm and 52 in the control arm. All 107 patients completed the 4-week treatment period and elected to enter the 96-week open-label extension study where all patients receive the VX-445 triple combination regimen.

Efficacy Results: As previously announced, data from this study showed a mean absolute improvement in $ppFEV_1$ of 10.0 percentage points from baseline at week 4 when VX-445 was added in patients who were already receiving tezacaftor in combination with ivacaftor compared to those in whom placebo was added to tezacaftor and ivacaftor ($p<0.0001$), which was the primary endpoint of the study. In addition, statistically significant improvements in both key secondary endpoints were observed at week 4 of the study. A summary of the Phase 3 efficacy data, including results announced today for key secondary endpoints, is provided below:

	Placebo/TEZ/IVA (n=52)	VX-445/TEZ/IVA (n=55)	Treatment Difference
Primary Endpoint*			
Absolute Change in ppFEV$_1$ from Baseline at Week 4	0.4	10.4	10.0 (p<0.0001)
Key Secondary Endpoints*			
Absolute Change in Sweat Chloride from Baseline at Week 4	1.7	-43.4	-45.1 (p<0.0001)
Absolute Change in CFQ-R Respiratory Domain from Baseline at Week 4	-1.4	16.0	17.4 (p<0.0001)

**Primary and secondary endpoints were evaluated as part of the final analysis*

Safety Results: The VX-445 triple combination was generally well tolerated in this 4-week study. The majority of adverse events were mild or moderate. Serious adverse events were observed in 3.6% (n=2) of the patients who received VX-445, tezacaftor and ivacaftor and in 1.9% (n=1) of the patients who received placebo, tezacaftor and ivacaftor. There were no adverse events that occurred in 15% or more of patients in either arm of the study. There were no discontinuations due to adverse events in either arm of the study.

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 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 cells 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'sInnovation District. Today, the company has research and development sites and commercial offices in the United States, Europe, Canada, Australia and Latin America. 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 nine 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™/SYMKEVI™ (tezacaftor/ivacaftor and ivacaftor), and VX-445 (elexacaftor) 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. Rowe's statements in the fourth paragraph, Dr. Kewalramani's statements in the fifth paragraph, and the information provided regarding (i) the plan to seek global regulatory approvals for a triple combination regimen in both F/MF and F/F populations, and (ii) the expected timing of the NDA and MAA submissions for the VX-445 triple combination regimen. 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 the company could experience unforeseen delays in submitting regulatory filings, that regulatory authorities may not approve, or approve on a timely basis, a triple-combination regimen 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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