Two Phase 3 Studies of the Triple Combination of VX-659, Tezacaftor and Ivacaftor Met Primary Endpoint of Improvement in Lung Function (ppFEV1) in People with Cystic Fibrosis

November 27, 2018

-Mean absolute improvement in ppFEV$_1$ of 14.0 percentage points from baseline at week 4 in people with one F508del mutation and one minimal function mutation compared to placebo (p<0.0001)-

-Mean absolute improvement in ppFEV$_1$ of 10.0 percentage points from baseline at week 4 when VX-659 was added in people with two F508del mutations already receiving tezacaftor and ivacaftor compared to control group of placebo added to tezacaftor and ivacaftor (p<0.0001)-

-Safety and efficacy profile supports potential submission of a New Drug Application for the VX-659 triple combination regimen-

-Two Phase 3 studies of the triple combination of VX-445, tezacaftor and ivacaftor are now fully enrolled with data expected in the first quarter of 2019-

BOSTON--(BUSINESS WIRE)--Nov. 27, 2018-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced that treatment with the triple combination of the next-generation corrector VX-659, tezacaftor and ivacaftor resulted in statistically significant improvements in lung function (percent predicted forced expiratory volume in one second, or ppFEV$_1$) in two Phase 3 studies in people with cystic fibrosis (CF). Data from a pre-specified interim analysis of the Phase 3 study in people with one *F508del* mutation and one minimal function mutation showed a mean absolute improvement in ppFEV$_1$ of 14.0 percentage points from baseline at week 4 of treatment compared to placebo (p<0.0001). In the Phase 3 study in people with two *F508del* mutations, the addition of VX-659 in patients already receiving tezacaftor and ivacaftor resulted in a mean absolute improvement in ppFEV$_1$ of 10.0 percentage points from baseline at week 4 of treatment compared to the control group in whom placebo was added to tezacaftor and ivacaftor (p<0.0001). The VX-659 triple combination regimen was generally well tolerated, and the safety and efficacy profile from the results released today supports the potential submission of a New Drug Application (NDA) for the VX-659 triple combination regimen.

Vertex also today announced that enrollment is complete for the two Phase 3 studies of the triple combination of the next-generation corrector VX-445, tezacaftor and ivacaftor in people with CF with one *F508del* mutation and one minimal function mutation and in people with two *F508del* mutations. Vertex remains on track to report topline data from both Phase 3 studies of the VX-445 triple combination regimen in the first quarter of 2019.

The data expected in the first quarter of 2019 for VX-445 and the data reported today for VX-659 will enable Vertex to choose the best regimen to submit for potential regulatory approvals globally and will provide the basis for potential submission of an NDA for a triple combination regimen to the U.S. FDA no later than mid-2019.

“These data mark a major milestone in our efforts to develop new CF medicines as they underscore the important clinical benefit that a triple combination regimen may provide to the vast majority of CF patients who have at least one *F508del* mutation,” said Reshma Kewalramani, M.D., Executive Vice President, Global Medicines Development and Medical Affairs and Chief Medical Officer at Vertex. “We plan to evaluate data for the VX-445 and VX-659 triple combination regimens in the first quarter of next year and to choose the best regimen to submit for potential approval with the goal of bringing forward a new treatment option to those with one *F508del* mutation and one minimal function mutation and to those with two *F508del* mutations as rapidly as possible.”

About the VX-659 Phase 3 Study in People with One *F508del* Mutation and One Minimal Function Mutation

The data announced today for people ages 12 and older with one *F508del* mutation and one minimal function mutation are from an ongoing, randomized, double-blind, placebo-controlled Phase 3 study evaluating the triple combination of VX-659, tezacaftor and ivacaftor compared to triple placebo for 24 weeks. The study randomized 385 patients, and 382 patients received at least one dose of either the VX-659 triple combination regimen or triple placebo. In the U.S., the primary endpoint of the study is the mean absolute change in ppFEV$_1$ from baseline at week 4 of triple combination treatment compared to triple placebo. The data announced today are from a pre-specified interim analysis that evaluated the primary endpoint at week 4. 380 patients had completed the week 4 visit of the study at the time of the interim analysis. The safety and efficacy profile in the interim analysis supports the potential submission of an NDA for the VX-659 triple combination regimen for patients with one *F508del* mutation and one minimal function mutation.

Topline Data:

Treatment with the triple combination of VX-659, tezacaftor and ivacaftor resulted in a mean absolute improvement in ppFEV$_1$ of 14.0 percentage points from baseline at week 4 compared to triple placebo (p<0.0001), which was the primary endpoint of the study. The mean absolute within-group improvement in ppFEV$_1$ for those who received the VX-659 triple combination regimen was 13.0 percentage points from baseline at week 4. The mean absolute within-group change in ppFEV$_1$ for those who received triple placebo was -1.0 percentage points from baseline at week 4.

The VX-659 triple combination regimen was generally well tolerated in this study, and the safety profile reflects all available safety data for all patients at the time of the interim analysis, including 302 patients who had reached the week 12 visit (151 patients who were randomized to receive the VX-659 triple combination regimen and 151 patients randomized to receive triple placebo) and 58 patients who had completed the 24-week treatment period (28 patients randomized to receive the VX-659 triple combination regimen and 30 patients randomized to receive triple placebo).

This study is ongoing to evaluate the VX-659 triple combination regimen for a total of 24 weeks and will generate additional safety and efficacy data and data for key secondary endpoints, including the number of pulmonary exacerbations, change in sweat chloride, change in patient-reported outcomes as measured by the respiratory domain score of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) and change in body mass index,

among others. To preserve the integrity of this ongoing study and the ongoing Phase 3 studies of VX-445, Vertex intends to wait to disclose additional safety and efficacy data for this study, including key secondary endpoints, until the second half of 2019 following the completion of the VX-659 and VX-445 Phase 3 studies.

Open-Label Extension Study:

All patients who complete treatment in the 24-week study, regardless of treatment assignment, are given the opportunity to enroll in a rollover study where all patients receive the VX-659 triple combination regimen. All patients who had completed the study at the time of the interim analysis elected to enter the open-label extension study.

About the VX-659 Phase 3 Study in People with Two *F508del* Mutations

The data announced today for people with two *F508del* mutations are from a randomized, double-blind, controlled Phase 3 study that evaluated four weeks of treatment with the triple combination of VX-659, tezacaftor, and ivacaftor compared to placebo, tezacaftor and ivacaftor. The study randomized 111 patients ages 12 years or older who have two *F508del* mutations. All patients received tezacaftor in combination with ivacaftor during a 4-week run-in prior to randomization, and all of the 111 patients who were randomized received at least 1 dose of either the triple combination of VX-659, tezacaftor and ivacaftor or placebo, tezacaftor and ivacaftor. The primary endpoint of the study was the mean absolute change in $ppFEV_1$ from baseline (end of the 4-week tezacaftor/ivacaftor run-in) at week 4 of triple combination of VX-659, tezacaftor and ivacaftor compared to placebo in combination with tezacaftor and ivacaftor. The data announced today reflect topline data from the primary efficacy and safety analysis conducted once all (n=111) patients completed the study. The safety and efficacy profile in this study supports the potential submission of an NDA for the VX-659 triple combination regimen for patients with two *F508del* mutations.

Topline Data:

Data from this study showed a mean absolute improvement in $ppFEV_1$ of 10.0 percentage points from baseline at week 4 when VX-659 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. The mean absolute within-group improvement in $ppFEV_1$ from baseline for those who received VX-659 in triple combination with tezacaftor and ivacaftor was 10.2 percentage points at week 4. The mean absolute within-group change in $ppFEV_1$ from baseline for those who received placebo, tezacaftor and ivacaftor was 0.3 percentage points at week 4.

The VX-659 triple combination regimen was generally well tolerated in this study. All of the 111 patients who were randomized in the study completed the 4-week triple combination treatment period.

To preserve the integrity of the ongoing Phase 3 studies of VX-659 and VX-445, Vertex intends to wait to disclose additional safety and efficacy data for this study, including key secondary endpoints, until the second half of 2019 following the completion of the VX-659 and VX-445 Phase 3 studies.

Open-Label Extension Study: Similar to the study in people with one *F508del* mutation and one minimal function mutation, all patients who completed treatment, regardless of treatment assignment, were given the opportunity to enroll in a rollover study where all patients received the VX-659 triple combination regimen. 110 of the 111 patients who completed the study elected to enter the open-label extension study.

Enrollment Complete for the VX-445 Phase 3 Studies

Vertex today announced that it has completed enrollment for the two Phase 3 studies evaluating the triple combination of VX-445, tezacaftor and ivacaftor in people with one *F508del* mutation and one minimal function mutation and in people with two *F508del* mutations. The study designs are the same as were used for the VX-659 Phase 3 program noted above.

Similar to the VX-659 program, the Phase 3 study of the VX-445 triple combination regimen in patients with one *F508del* mutation and one minimal function mutation was designed with a pre-specified interim analysis to evaluate the U.S. primary endpoint of $ppFEV_1$ at week 4. Data from the VX-445 interim analysis are expected in the first quarter of 2019. Similar to VX-659, Vertex expects to disclose in the first quarter of 2019 only the topline results for the primary 4-week efficacy endpoints of the VX-445 Phase 3 studies and whether the safety and efficacy profile observed supports a potential NDA submission. Vertex intends to disclose additional safety and efficacy data, including key secondary endpoints, for the VX-445 studies in the second half of 2019 following the completion of the VX-659 and VX-445 Phase 3 studies.

Submissions for Approval Outside the U.S.

Data from these studies of VX-659 and VX-445 will also be used for regulatory submissions outside of the U.S. planned for late 2019.

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® (tezacaftor/ivacaftor and ivacaftor), 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. Kewalramani's statements in the fourth paragraph, and the information provided regarding (i) the company's plans regarding announcement of additional data from its ongoing studies, including topline data from the ongoing VX-445 triple combination study and (ii) the company's plans regarding the potential submission of regulatory filings for its triple combination regimens in the U.S. and outside of the U.S. 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 topline data reported in this press release is based on a pre-specified interim analysis of the ongoing VX-659 triple combination studies and that final data may differ, that the VX-445 triple combination study is ongoing, 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.

(VRTX-GEN)

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