Two Phase 3 Studies of the Triple Combination of VX-445, Tezacaftor and Ivacaftor Met Primary Endpoint of Improvement in Lung Function (ppFEV1) in People with Cystic Fibrosis

March 6, 2019

-Mean absolute improvement in ppFEV$_1$ of 13.8 percentage points from baseline at week 4 in people with one F508del mutation and one minimal function mutation (F/MF) compared to placebo (p<0.0001)-

-Mean absolute improvement in ppFEV$_1$ of 10.0 percentage points from baseline at week 4 when VX-445 was added in people with two F508del mutations (F/F) already receiving tezacaftor and ivacaftor compared to control group of placebo added to tezacaftor and ivacaftor (p<0.0001)-

-Safety and efficacy profile reported today supports potential submission of a New Drug Application for the VX-445 triple combination regimen-

-Vertex plans to seek global regulatory approvals for either VX-659 or VX-445 triple combination regimen in both F/F and F/MF patient populations concurrently based on final 24-week data for both regimens expected in the second quarter of 2019-

-U.S. NDA and EU MAA planned for the third and fourth quarters of 2019, respectively-

BOSTON--(BUSINESS WIRE)--Mar. 6, 2019-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced that treatment with the triple combination of the next-generation corrector VX-445, 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 13.8 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-445 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-445 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-445 triple combination regimen.

The Phase 3 data announced today for the VX-445 triple combination regimen follow Phase 3 data announced in late 2018 for the triple combination of VX-659, tezacaftor and ivacaftor that also showed a safety and efficacy profile supportive of a potential NDA submission. Given the similarity of the data for the 4-week primary efficacy endpoint for the VX-659 and VX-445 regimens and the near-term availability of the final 24-week data for both regimens in the second quarter of 2019, Vertex plans to utilize these final 24-week data to choose the best regimen to submit for regulatory approvals globally. Because these submissions will include the final 24-week data, Vertex will seek approval for patients ages 12 and older with one *F508del* mutation and one minimal function mutation and for patients with two *F508del* mutations concurrently. Vertex plans to submit an NDA to the U.S. FDA in the third quarter of 2019 and a Marketing Authorization Application (MAA) in Europe in the fourth quarter of 2019 for either the VX-659 or VX-445 triple combination regimen. The company also plans to disclose more detailed data from the Phase 3 studies of the selected triple combination regimen, including 24-week data from the study in patients with one *F508del* mutation and one minimal function mutation, in the second quarter of 2019.

“Both the VX-659 and VX-445 triple combination regimens showed highly consistent and significant improvements in lung function across our Phase 3 programs, underscoring the important clinical benefit that a triple combination regimen may provide to patients with two *F508del* mutations and to those with one *F508del* and one minimal function mutation,” said Reshma Kewalramani, M.D., Executive Vice President, Global Medicines Development and Medical Affairs and Chief Medical Officer at Vertex. “We look forward to submitting global regulatory applications for one of these triple combination regimens for both patient populations later this year.”

About the VX-445 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-445, tezacaftor and ivacaftor compared to triple placebo for 24 weeks. The study randomized 405 patients, and 403 patients received at least one dose of either the VX-445 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. 402 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-445 triple combination regimen for patients with one *F508del* mutation and one minimal function mutation.

Topline Data:

Treatment with the triple combination of VX-445, tezacaftor and ivacaftor 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. The mean absolute within-group improvement in ppFEV$_1$ for those who received the VX-445 triple combination regimen was 13.6 percentage points from baseline at week 4. The mean absolute within-group change in ppFEV$_1$ for those who received triple placebo was -0.2 percentage points from baseline at week 4.

The VX-445 triple combination regimen was generally well tolerated in this study. The safety profile reflects all available safety data for all patients at the time of the interim analysis, including 246 patients who had reached the week 12 visit (123 patients who were randomized to the VX-445 triple combination regimen and 123 patients randomized to triple placebo) and 65 patients who had completed the 24-week treatment period (29 patients

randomized to receive the VX-445 triple combination regimen and 36 patients randomized to receive triple placebo).

This study is ongoing to evaluate the VX-445 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.

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-445 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-445 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-445, tezacaftor, and ivacaftor compared to placebo, tezacaftor and ivacaftor. The study randomized 108 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 107 of the 108 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-445, 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=107) patients completed the study. The safety and efficacy profile in this study supports the potential submission of an NDA for the VX-445 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-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. The mean absolute within-group improvement in $ppFEV_1$ from baseline for those who received VX-445 in triple combination with tezacaftor and ivacaftor was 10.4 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 0.4 percentage points at week 4.

The VX-445 triple combination regimen was generally well tolerated in this study. All of the 107 patients who received either the triple combination of VX-445, tezacaftor and ivacaftor or placebo, tezacaftor and ivacaftor completed the 4-week triple combination treatment period.

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-445 triple combination regimen. All 107 of the patients who completed the study elected to enter the open-label extension 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® (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 third 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, (ii) the expected timing of the NDA and MAA submissions for a triple combination therapy and (iii) the plan to provide additional data regarding the selected regimen in the second quarter of 2019. 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 triple combination studies are 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.

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