Vertex Completes Enrollment of Two Phase 3 Studies of VX-659 in Triple Combination with Tezacaftor and Ivacaftor for the Treatment of Cystic Fibrosis

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-Data expected in late 2018 from Phase 3 studies of VX-659, tezacaftor and ivacaftor in people with one F508del mutation and one minimal function mutation and in people with two F508del mutations-

-Enrollment of two Phase 3 studies of VX-445 in triple combination with tezacaftor and ivacaftor expected to be complete in the fourth quarter of 2018; Data for both studies of VX-445, tezacaftor and ivacaftor expected in the first quarter of 2019-

-Vertex plans to evaluate VX-659 and VX-445 triple combination data to choose the best regimen to submit for potential regulatory approval; Submission of New Drug Application planned for no later than mid-2019-

BOSTON--(BUSINESS WIRE)--Sep. 6, 2018-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced that enrollment is complete for the two Phase 3 studies of the next-generation corrector VX-659 in triple combination with tezacaftor and ivacaftor in people with cystic fibrosis (CF) with one *F508del* mutation and one minimal function mutation and in people with two *F508del* mutations. Based on the completion of enrollment, Vertex expects to report data from both Phase 3 studies of the VX-659 triple combination regimen in late 2018. Vertex expects to complete enrollment of the two Phase 3 studies of the next-generation corrector VX-445 in triple combination with tezacaftor and ivacaftor in the fourth quarter of 2018 and to report data from these studies in the first quarter of 2019. Vertex plans to evaluate data from both the VX-659 and VX-445 Phase 3 triple combination programs to choose the best regimen to submit for potential regulatory approval. The data expected in late 2018 for VX-659 and in the first quarter of 2019 for VX-445 are expected to provide the basis for submission of a New Drug Application (NDA) to the U.S. FDA for people with one *F508del* mutation and one minimal function mutation no later than mid-2019.

"The two Phase 3 studies of VX-659, tezacaftor and ivacaftor enrolled nearly 500 people with CF in less than five months, underscoring the significant interest within the CF community to advance triple combination regimens that have the potential to treat up to 90 percent of all people with the disease," Reshma Kewalramani, M.D., Executive Vice President, Global Medicines Development and Medical Affairs and Chief Medical Officer at Vertex. "Our goal is to bring the best triple combination regimen to people with CF as quickly as possible, and we look forward to obtaining data later this year and in the first quarter of 2019 to support a submission for potential approval of a triple combination regimen."

The Phase 3 study of the VX-659 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 primary endpoint of $ppFEV_1$ at 4 weeks and safety through 12 weeks. This interim analysis will be conducted once all patients are through the primary efficacy endpoint at week 4. These efficacy and safety data from the interim analysis are expected in late 2018 and are intended to support a potential NDA submission for the VX-659, tezacaftor and ivacaftor triple combination regimen in people with one *F508del* mutation and one minimal function mutation.

Similar to the interim analysis for the VX-659 triple combination regimen, 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 primary endpoint of $ppFEV_1$ at 4 weeks and safety through 12 weeks. This interim analysis will also be conducted once all patients are through the primary efficacy endpoint at week 4. Data from the VX-445 interim analysis are expected in the first quarter of 2019. The interim analyses for the VX-659 and VX-445 triple combination regimens will enable Vertex to evaluate comparable data from both Phase 3 triple combination programs and determine the best regimen to submit for potential regulatory approval.

To preserve the integrity of the Phase 3 studies of VX-659, tezacaftor and ivacaftor and the Phase 3 studies of VX-445, tezacaftor and ivacaftor that will be ongoing into mid-2019, Vertex expects to disclose in late 2018 and the first quarter of 2019 only the topline results for the primary 4-week efficacy endpoints of the VX-659 and VX-445 Phase 3 studies, respectively, and whether the safety and efficacy profiles observed support a potential NDA submission. In the second half of 2019, Vertex intends to disclose additional safety and efficacy data, including secondary endpoints, for each study following the completion of both the VX-659 and VX-445 Phase 3 triple combination programs.

About the VX-659 Phase 3 Study in People with One *F508del* Mutation and One Minimal Function Mutation
The ongoing randomized, double-blind, placebo-controlled Phase 3 study is evaluating VX-659 in triple combination with tezacaftor and ivacaftor, or triple placebo, in 385 patients ages 12 and older who have one F508del mutation and one minimal function mutation. The primary endpoint of the study is the mean absolute change in percent predicted forced expiratory volume in one

second ($ppFEV_1$) from baseline at week 4 of triple combination treatment compared to triple placebo. The study was designed to include a pre-specified interim analysis to evaluate the primary endpoint at 4 weeks and safety through 12 weeks. This interim analysis will be conducted once all patients are through the primary efficacy endpoint at week 4. These data are expected to form the basis of a potential NDA submission to the U.S. FDA for people with one *F508del* mutation and one minimal function mutation. The study is evaluating VX-659 in combination with tezacaftor and ivacaftor for a total of 24 weeks of treatment and will generate additional safety data and data for key secondary endpoints, including the number of pulmonary exacerbations, change in body mass index, change in sweat chloride, and change in patient-reported outcomes as measured by the respiratory domain score of the Cystic Fibrosis Questionnaire-Revised (CFQ-R), among others.

About the VX-659 Phase 3 Study in People with Two *F508del* Mutations
The randomized, double-blind, controlled Phase 3 study evaluated four weeks of treatment with VX-659 or placebo in combination with tezacaftor and ivacaftor in 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 the start of the triple combination treatment period. The primary endpoint of the study is the mean absolute change in $ppFEV_1$ from baseline (end of the 4-week tezacaftor/ivacaftor run-in) at week four of treatment with VX-659 in triple combination with tezacaftor and ivacaftor compared to those who receive placebo, tezacaftor and ivacaftor.

About the VX-445 Phase 3 Studies
Vertex expects to complete enrollment in the fourth quarter of 2018 for two Phase 3 studies evaluating VX-445 in triple combination with tezacaftor and ivacaftor in people with one *F508del* mutation and one minimal function mutation and in people with two *F508del* mutations. The study designs, including the pre-specified interim analysis for the study in people with one *F508del* mutation and one minimal function mutation, are the same as were used for the VX-659 Phase 3 program noted above.

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 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-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 second paragraph and the information provided regarding (i) the timing of expected data from the Phase 3 studies of VX-659 and VX-445, (ii) the timing of expected completion of enrollment for the Phase 3 studies of VX-445, (iii) the company's expectation that it will evaluate VX-659 and VX-445 data to choose the best regimen to submit for potential regulatory approval no later than mid-2019, (iv) information regarding the planned interim analysis and (v) information regarding the timing and type of data the company intends to disclose from the Phase 3 studies. 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 that data from the Phase 3 development programs may not support continued development or approval of the company's triple-combination regimens 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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