Positive Phase 3 Study Results for TRIKAFTA® (elexacaftor/tezacaftor /ivacaftor and ivacaftor) in People Ages 12 and Older With Cystic Fibrosis Who Have One Copy of the F508del Mutation and One Gating or Residual Function Mutation

July 20, 2020

-Phase 3 study met primary endpoint and all secondary endpoints-

-Study is a U.S. post-marketing commitment and will be submitted to FDA-

-Data also will be submitted to the European Medicines Agency to support indication expansion of the EU label following triple combination approval-

BOSTON--(BUSINESS WIRE)--Jul. 20, 2020-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced results of a global Phase 3 study of TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor) in people with cystic fibrosis (CF) ages 12 years and older who have one copy of the *F508del* mutation and one gating mutation (F/G) or one copy of the *F508del* mutation and one residual function mutation (F/RF). The study met its primary endpoint of mean absolute within-group change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline through 8 weeks of treatment, demonstrating a statistically significant 3.7 percentage point ($p<0.0001$) improvement in $ppFEV_1$ in patients treated with TRIKAFTA compared to their baseline after a 4-week run-in of treatment on ivacaftor or tezacaftor/ivacaftor. The study met all secondary endpoints, including a statistically significant mean within-group reduction of 22.3 mmol/L from baseline in sweat chloride ($p<0.0001$). The regimen was generally well-tolerated, and safety data were consistent with those observed in previous Phase 3 studies with TRIKAFTA.

The study is a post-marketing commitment in the U.S. and the results will be submitted to the U.S. Food and Drug Administration. In the U.S., TRIKAFTA is already approved for use in people with CF ages 12 years and older who have at least one copy of the *F508del* mutation, which includes the populations evaluated in this study. In June, Vertex received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) for the initial triple combination regimen application for people with CF ages 12 years and older with one *F508del* mutation and one minimal function mutation (F/MF) or two *F508del* mutations (F/F). Data announced today from this study will be submitted to the European Medicines Agency to support a potential indication expansion of the EU label, once European Commission approval has been granted for the initial triple combination application. Full study results will be submitted for presentation at a future medical meeting and/or publication.

“The results of this study demonstrate that the triple combination provides significant additional benefit compared to existing CFTR modulator therapy for F/G and F/RF patients and adds to the robust body of evidence supporting the benefit of this medicine for patients with at least one *F508del* mutation,” said Carmen Bozic, M.D., Executive Vice President, Global Medicines Development and Medical Affairs, and Chief Medical Officer at Vertex. “We look forward to submitting these data to the EMA in support of a potential indication expansion of the EU label following initial approval.”

About the 445-104 Study

The data announced today are from a global Phase 3, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of TRIKAFTA in people with CF ages 12 years and older who have one copy of the *F508del* mutation and one gating mutation (F/G), or one copy of the *F508del* mutation and one residual function mutation (F/RF). All participants had a 4-week run-in period of either ivacaftor or tezacaftor/ivacaftor. Following the run-in, patients were randomized to receive TRIKAFTA or to remain on their prior regimen of ivacaftor or tezacaftor/ivacaftor for 8 weeks. Baseline was measured at the end of the run-in period, prior to the start of the 8-week treatment period. A total of 132 participants received TRIKAFTA and 126 patients were in the control group that received either ivacaftor or tezacaftor/ivacaftor.

The primary endpoint of the study, the mean absolute within-group improvement from baseline in $ppFEV_1$ through 8 weeks of treatment with TRIKAFTA, demonstrated a statistically significant improvement of +3.7 percentage points in $ppFEV_1$ ($p<0.0001$).

The study met all secondary endpoints, including, in the order of statistical testing hierarchy, statistically significant mean absolute within-group change in sweat chloride of -22.3 mmol/L ($p<0.0001$) from baseline through 8 weeks in patients treated with TRIKAFTA, and between-group mean changes of +3.5 percentage points in $ppFEV_1$ ($p<0.0001$) and -23.1 mmol/L in sweat chloride ($p<0.0001$) in patients treated with TRIKAFTA compared to the control group of those who received ivacaftor or tezacaftor/ivacaftor.

Overall, safety data were similar to those observed in previous Phase 3 studies of TRIKAFTA, and the regimen was generally well tolerated. The majority of adverse events were mild or moderate. The most common adverse event that occurred in 15% or more patients, regardless of treatment arm, was headache. Serious adverse events were observed in 3.8% (n=5) of the patients who received TRIKAFTA and in 8.7% (n=11) of the patients who received ivacaftor or tezacaftor/ivacaftor. In the study, 2 patients taking ivacaftor or tezacaftor/ivacaftor and 1 patient taking TRIKAFTA discontinued treatment due to adverse events.

About Cystic Fibrosis

Cystic Fibrosis (CF) is a rare, life-shortening genetic disease affecting approximately 75,000 people worldwide. CF is a progressive, multi-system disease that affects the lungs, liver, GI tract, sinuses, sweat glands, pancreas and reproductive tract. CF is caused by a defective and/or missing CFTR protein resulting from certain mutations in the *CFTR* gene. Children must inherit two defective *CFTR* genes — one from each parent — to have CF. While there are many different types of *CFTR* mutations that can cause the disease, the vast majority of all people with CF have at least one *F508del* mutation. These mutations, which can be determined by a genetic test, or genotyping test, lead to CF by creating non-working and/or too few CFTR proteins at the cell surface. The defective function and/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 early 30s.

About TRIKAFTA®

TRIKAFTA (elexacaftor/tezacaftor/ivacaftor and ivacaftor) is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients ages 12 years and older who have at least one copy of the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Patients should talk to their doctor to learn if they have an indicated CF gene mutation. It is not known if TRIKAFTA is safe and effective in children under 12 years of age. TRIKAFTA is designed to increase the quantity and function of the F508del-CFTR protein at the cell surface. The approval of TRIKAFTA was supported by positive results of two global Phase 3 studies in people ages 12 years and older with CF: a 24-week Phase 3 study in 403 people with one *F508del* mutation and one minimal function mutation (F/MF) and a 4-week Phase 3 study in 107 people with two *F508del* mutations (F/F).

U.S. INDICATION AND IMPORTANT SAFETY INFORMATION FOR TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor) TABLETS

TRIKAFTA is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one copy of the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Patients should talk to their doctor to learn if they have an indicated CF gene mutation. It is not known if TRIKAFTA is safe and effective in children under 12 years of age.

Patients should not take TRIKAFTA if they take certain medicines, such as: antibiotics such as rifampin or rifabutin; seizure medicines such as phenobarbital, carbamazepine, or phenytoin; St. John's wort.

Before taking TRIKAFTA, patients should tell their doctor about all of their medical conditions, including if they: have kidney problems, have or have had liver problems, are pregnant or plan to become pregnant because it is not known if TRIKAFTA will harm an unborn baby, or are breastfeeding or planning to breastfeed because it is not known if TRIKAFTA passes into breast milk.

TRIKAFTA may affect the way other medicines work, and other medicines may affect how TRIKAFTA works. Therefore, the dose of TRIKAFTA may need to be adjusted when taken with certain medicines. Patients should especially tell their doctor if they take: antifungal medicines including ketoconazole, itraconazole, posaconazole, voriconazole, or fluconazole; antibiotics including telithromycin, clarithromycin, or erythromycin; other medicines including rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort.

TRIKAFTA may cause dizziness in some people who take it. Patients should not drive a car, operate machinery, or do anything that requires alertness until they know how TRIKAFTA affects them.

Patients should avoid food or drink that contains grapefruit while they are taking TRIKAFTA.

TRIKAFTA can cause serious side effects, including:

High liver enzymes in the blood, which is a common side effect in people treated with TRIKAFTA**.** These can be serious and may be a sign of liver injury. The patient's doctor will do blood tests to check their liver before they start TRIKAFTA, every 3 months during the first year of taking TRIKAFTA, and every year while taking TRIKAFTA. Patients should call their doctor right away if they have any of the following symptoms of liver problems: pain or discomfort in the upper right stomach (abdominal) area; yellowing of the skin or the white part of the eyes; loss of appetite; nausea or vomiting; dark, amber-colored urine.

Abnormality of the eye lens (cataract) in some children and adolescents treated with TRIKAFTA. If the patient is a child or adolescent, their doctor should perform eye examinations before and during treatment with TRIKAFTA to look for cataracts.

The most common side effects of TRIKAFTA include headache, diarrhea, upper respiratory tract infection (common cold) including stuffy and runny nose, stomach (abdominal) pain, inflamed sinuses, increase in liver enzymes, increase in a certain

blood enzyme called creatine phosphokinase, rash, flu (influenza), and increase in blood bilirubin.

These are not all the possible side effects of TRIKAFTA. **Please click here to see the full Prescribing Information for TRIKAFTA.**

About Vertex

Vertex is a global biotechnology company that invests in scientific innovation to create transformative medicines for people with serious diseases. The company has multiple approved medicines that treat the underlying cause of cystic fibrosis (CF) — a rare, life-threatening genetic disease — and has several ongoing clinical and research programs in CF. Beyond CF,Vertex has a robust pipeline of investigational small molecule medicines in other serious diseases where it has deep insight into causal human biology, including pain, alpha-1 antitrypsin deficiency, and APOL1-mediated kidney diseases. In addition, Vertex has a rapidly expanding pipeline of genetic and cell therapies for diseases such as sickle cell disease, beta thalassemia, Duchenne muscular dystrophy and type 1 diabetes mellitus.

Founded in 1989 in Cambridge, Mass., Vertex's global headquarters is now located in Boston's Innovation District and its international headquarters is in London, UK. Additionally, the company has research and development sites and commercial offices in North America, Europe, Australia and Latin America. Vertex is consistently recognized as one of the industry's top places to work, including 10 consecutive years on Science magazine's Top Employers list and top five on the 2019 Best Employers for Diversity list by Forbes. For company updates and to learn more about Vertex's history of innovation, visit www.vrtx.com or follow us on Facebook, Twitter, LinkedIn, YouTube and Instagram.

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, statements made by Dr. Carmen Bozic in this press release, statements regarding the potential benefits of TRIKAFTA and our plans to submit data and full study results, and our expectations regarding potential approval for the triple combination regimen and a potential expansion of the EU label. 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 risks and uncertainties that could cause actual events or results to differ materially from those expressed or implied by such forward-looking statements. Those risks and uncertainties include, among other things, that data from the company's development programs may not support registration or further development of its compounds due to safety, efficacy or other reasons, risks related to approval and commercialization of our medicines, and other risks listed under Risk Factors in Vertex's annual report and subsequent 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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