Positive Phase 3 Study for Tezacaftor/Ivacaftor Combination in Children Aged 6-11 Years with Cystic Fibrosis Supports European Medicines Agency Submission

February 14, 2019

-Study met primary endpoint with a statistically significant improvement in absolute change in lung clearance index ($LCI_{2.5}$) through 8 weeks of tezacaftor/ivacaftor treatment-

-Tezacaftor in combination with ivacaftor was generally well tolerated and safety data were consistent with previous studies-

-Data support a submission to the European Medicines Agency in the second half of 2019-

BOSTON--(BUSINESS WIRE)--Feb. 14, 2019-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced the results of a Phase 3 study conducted in Europe and Australia of tezacaftor in combination with ivacaftor in children aged 6 through 11 years with cystic fibrosis (CF) who have either two copies of the *F508del* mutation or one copy of the *F508del* mutation and one residual function mutation. The study met its primary endpoint of absolute change in lung clearance index ($LCI_{2.5}$) through 8 weeks of treatment, demonstrating a statistically significant improvement in $LCI_{2.5}$ among patients treated with tezacaftor/ivacaftor. The regimen was generally well tolerated and safety data were consistent with those observed in previous studies with tezacaftor/ivacaftor. This efficacy study was designed to support a submission to the European Medicines Agency (EMA) to extend the indication of tezacaftor/ivacaftor in this patient population. Vertex plans to submit the application in the second half of 2019. In late 2018, Vertex submitted an sNDA to the U.S. Food and Drug Administration (FDA) for tezacaftor/ivacaftor based on a previously completed Phase 3 safety study in children ages 6 through 11 years of age conducted in the U.S. and Canada.

“These data mark an important milestone in our efforts to expand treatment options for patients living with CF,” said Reshma Kewalramani, M.D., Executive Vice President and Chief Medical Officer at Vertex. “We plan to submit an indication extension to the EMA in the second half of 2019, bringing us a step closer to potentially providing more children with a treatment option that addresses the underlying cause of the disease.”

Summary of Key Data

The data announced today are from a Phase 3, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of tezacaftor in combination with ivacaftor in children ages 6 through 11 who have either two copies of the *F508del* mutation or one copy of the *F508del* mutation and one residual function mutation. Subjects were randomized 4:1 based on their genotype to tezacaftor/ivacaftor versus a blinding arm (placebo for those with two copies of *F508del*; ivacaftor for those with one copy of *F508del* mutation and one residual function mutation). The study randomized and treated 54 subjects with TEZ/IVA, 10 with placebo, and 3 with ivacaftor.

The primary endpoint of the study was the within-group absolute change in lung clearance index ($LCI_{2.5}$) from baseline through Week 8 in patients treated with tezacaftor/ivacaftor. $LCI_{2.5}$ measures the efficiency of ventilation in the lungs by quantifying how many standard lung volumes it takes to reduce exhaled nitrogen to 2.5 percent of its starting value when breathing pure oxygen. LCI is considered a more sensitive measure to detect early lung disease than forced expiratory volume in one second (FEV_1). Higher LCI scores indicate poorer lung function. To participate in the study, children at an initial screening visit had to have an $LCI_{2.5} \geq 7.5$, which is considered the cutoff for abnormal gas exchange. In the study, 54 children that were treated with tezacaftor/ivacaftor experienced a mean within-group absolute improvement in $LCI_{2.5}$ of -0.51 through 8 weeks ($p < 0.0001$).

Overall, safety data were similar to those observed in previous studies of tezacaftor/ivacaftor. The most common adverse events (≥ 10%) among those patients receiving tezacaftor/ivacaftor were cough, headache, and productive cough. No serious adverse events or adverse events leading to treatment discontinuation or interruption were observed.

About Cystic Fibrosis

Cystic Fibrosis (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 cystic fibrosis transmembrane conductance regulator (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 cell 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 SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)

Some mutations result in CFTR protein that is not processed or folded normally within the cell, and that generally does not reach the cell surface. SYMDEKO is a combination of tezacaftor and ivacaftor. Tezacaftor is designed to address the trafficking and processing defect of the CFTR protein to enable it to reach the cell surface where ivacaftor can increase the amount of time the protein stays open.

U.S. INDICATION AND IMPORTANT SAFETY INFORMATION FOR SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) tablets

SYMDEKO is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have two copies of the *F508del* mutation, or who have at least one mutation in the CF gene that is responsive to treatment with SYMDEKO. Patients should talk to their doctor to learn if they have an indicated CF gene mutation. It is not known if SYMDEKO is safe and effective in children under 12 years of age.

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

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

SYMDEKO may affect the way other medicines work, and other medicines may affect how SYMDEKO works. Therefore, the dose of SYMDEKO may need to be adjusted when taken with certain medicines. Patients should especially tell their doctor if they take antifungal medicines such as ketoconazole, itraconazole, posaconazole, voriconazole, or fluconazole; or antibiotics such as telithromycin, clarithromycin, or erythromycin.

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

Patients should avoid food or drink that contains grapefruit or Seville oranges while they are taking SYMDEKO.

SYMDEKO can cause serious side effects, including:

High liver enzymes in the blood, which have been reported in people treated with SYMDEKO or treated with ivacaftor alone. The patient's doctor will do blood tests to check their liver before they start SYMDEKO, every 3 months during the first year of taking SYMDEKO, and every year while taking SYMDEKO. 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 SYMDEKO or with ivacaftor alone. If the patient is a child or adolescent, their doctor should perform eye examinations before and during treatment with SYMDEKO to look for cataracts.

The most common side effects of SYMDEKO include headache, nausea, sinus congestion, and dizziness.

These are not all the possible side effects of SYMDEKO. **Please click here to see the fullU.S.Prescribing Information for SYMDEKO (tezacaftor/ivacaftor and ivacaftor) tablets.**

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, the statements in the first paragraph of the press release and quote by Dr. Kewalramani in the second paragraph. 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 data from the company's development programs may not support registration or further development of its compounds 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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