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Positive Phase 3 Study of ORKAMBI® in Children With Cystic Fibrosis Ages 6-11 Who Have Two Copies of the F508del Mutation Supports a Submission to the European Medicines Agency in the First Half of 2017

- Study met primary endpoint with a statistically significant improvement in absolute change in lung clearance index ($LCI_{2.5}$) compared to placebo through 24 weeks of treatment -

- ORKAMBI was well tolerated with safety data that were similar to data from previous Phase 3 open-label safety study -

- Approximately 3,400 children ages 6-11 have two copies of the F508del mutation in Europe -

BOSTON--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq:VRTX) today announced the results of a Phase 3 study of ORKAMBI® (lumacaftor/ivacaftor) in children with cystic fibrosis (CF) ages 6 through 11 who have two copies of the *F508del* mutation. The study met its primary endpoint of absolute change in lung clearance index ($LCI_{2.5}$) through 24 weeks of treatment, demonstrating a statistically significant improvement in $LCI_{2.5}$ among patients treated with ORKAMBI compared to placebo. LCI is a sensitive measure of lung function in early CF disease and the European Medicines Agency (EMA) agreed to the primary endpoint for this study. In the first half of 2017, Vertex plans to submit a Marketing Authorization Application (MAA) line extension to the EMA for the use of ORKAMBI in this patient population. Data from a previous Phase 3 open-label safety study in children ages 6 through 11 supported the U.S. Food and Drug Administration approval of ORKAMBI in September 2016. In this second study, ORKAMBI was well tolerated with safety data that were similar to data from the previous Phase 3 study. There are approximately 3,400 children ages 6 through 11 who have two copies of the *F508del* mutation in Europe.

"This study is an important complement to recently presented long-term data in patients 12 years and older suggesting ORKAMBI may modify the course of CF. These new data demonstrate that treating the underlying cause of the disease with ORKAMBI improves lung function in even younger patients," said Jeffrey Chodakewitz, M.D., Executive Vice President and Chief Medical Officer at Vertex. "We are preparing to submit these important data to the EMA in the first half of 2017, and we look forward to bringing ORKAMBI to eligible children in Europe as soon as possible."

"CF is a progressive disease that begins at birth, and traditional measurements do not always detect the early lung damage that occurs in children," said Felix Ratjen, M.D., Division Chief of Pediatric Respiratory Medicine at The Hospital for Sick Children Toronto, Professor of Pediatrics at The University of Toronto, a Senior Scientist at the Research Institute in the Department of Physiology and Experimental Medicine, and Principal Investigator for the study. "LCI is a sensitive measure of lung function, and these new data demonstrate that treating children early with ORKAMBI can improve lung function."

Summary of Key Data

The data announced today are from a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of ORKAMBI in children ages 6 through 11 who have two copies of the *F508del* mutation. The study compared children who received treatment with lumacaftor (200 mg q12h) in combination with ivacaftor (250 mg q12h) (n=103) with those who received placebo (n=101) for 24 weeks. Baseline lung function as measured by percent predicted forced expiratory volume in one second ($ppFEV_1$) was 89.8.

The primary endpoint of the study was absolute change in lung clearance index ($LCI_{2.5}$) from baseline through Week 24. $LCI_{2.5}$ measures the efficiency of ventilation in the lungs by quantifying how long it takes to reduce an inhaled tracer gas to 2.5 percent of its starting value. 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 had to have an $LCI_{2.5}$ ≥7.5 at the initial screening visit, considered the cutoff for abnormal gas exchange. At baseline, mean $LCI_{2.5}$ was 10.28. In the study, children treated with ORKAMBI experienced an improvement in lung function ($LCI_{2.5}$) of -1.09 compared to placebo through 24 weeks ($p < 0.0001$).

Improvements in secondary endpoints were also observed in this study, including a statistically significant reduction in sweat chloride assessed by the average absolute change from baseline at Day 15 and Week 4 (-20.8 mmol/L compared to placebo; $p < 0.0001$). Improvements in body mass index (BMI) and the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score were also observed, although not statistically significant. The improvement in absolute change from baseline in body mass index (BMI) at Week 24 was 0.11 kg/m^2 compared to placebo (p=0.2522) and the improvement in absolute change from baseline in CFQ-R respiratory domain score through Week 24 was 2.5 points compared to placebo (p=0.0628). Lung function as assessed by an absolute change from baseline in $ppFEV_1$ through Week 24 was an additional endpoint of the study for which a statistically significant improvement of 2.4 percentage points compared to placebo (p=0.0182) was observed.

Overall, safety data were similar to those observed in a previous Phase 3 open-label safety study in children ages 6 through 11. In this study, the most common adverse events that occurred more frequently among those receiving ORKAMBI compared to placebo were infective pulmonary exacerbation, productive cough, nasal congestion, oropharyngeal pain, abdominal pain upper, headache, upper respiratory tract infection and sputum increased. The incidence of liver enzyme elevations and respiratory events were slightly higher in the ORKAMBI group compared to placebo. Treatment discontinuations due to adverse events were low across those receiving placebo (n=2) and those receiving ORKAMBI (n=3) through 24 weeks.

INDICATION AND IMPORTANT SAFETY INFORMATION FOR ORKAMBI® (lumacaftor/ivacaftor) TABLETS

ORKAMBI is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have two copies of the *F508del* mutation (*F508del/F508del*) in their CFTR gene. ORKAMBI should only be used in these patients. It is not known if ORKAMBI is safe and effective in children under 6 years of age.

Patients should not take ORKAMBI if they are taking certain medicines or herbal supplements, such as: the antibiotics rifampin or rifabutin; the seizure medicines phenobarbital, carbamazepine, or phenytoin; the sedatives/anti-anxiety medicines triazolam or midazolam; the immunosuppressant medicines everolimus, sirolimus, or tacrolimus; or St. John's wort.

Before taking ORKAMBI, patients should tell their doctor if they: have or have had liver problems; have kidney problems; have had an organ transplant; are using birth control (hormonal contraceptives, including oral, injectable, transdermal or implantable forms). Hormonal contraceptives should not be used as a method of birth control when taking ORKAMBI. Patients should tell their doctor if they are pregnant or plan to become pregnant (it is unknown if ORKAMBI will harm the unborn baby) or if they are breastfeeding or planning to breastfeed (it is unknown if ORKAMBI passes into breast milk).

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

When taking ORKAMBI, patients should tell their doctor if they stop ORKAMBI for more than 1 week as the doctor may need to change the dose of ORKAMBI or other medicines the patient is taking. It is unknown if ORKAMBI causes dizziness. Patients should not drive a car, use machinery, or do anything requiring alertness until the patient knows how ORKAMBI affects them.

ORKAMBI can cause serious side effects including:

High liver enzymes in the blood, which can be a sign of liver injury, have been reported in patients receiving ORKAMBI. The patient's doctor will do blood tests to check their liver before they start ORKAMBI, every three months during the first year of taking ORKAMBI, and annually thereafter. The patient should call the 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; or confusion.

Respiratory events such as shortness of breath or chest tightness were observed in patients when starting ORKAMBI. If a patient has poor lung function, their doctor may monitor them more closely when starting ORKAMBI.

An increase in blood pressure has been seen in some patients treated with ORKAMBI. The patient's doctor should monitor their blood pressure during treatment with ORKAMBI.

Abnormality of the eye lens (cataract) has been noted in some children and adolescents receiving ORKAMBI

and ivacaftor, a component of ORKAMBI. For children and adolescents, the patient's doctor should perform eye examinations prior to and during treatment with ORKAMBI to look for cataracts.

The most common side effects of ORKAMBI include: shortness of breath and/or chest tightness; upper respiratory tract infection (common cold), including sore throat, stuffy or runny nose; gastrointestinal symptoms including nausea, diarrhea, or gas; rash; fatigue; flu or flu-like symptoms; increase in muscle enzyme levels; and irregular, missed, or abnormal menstrual periods and heavier bleeding.

Please click here to see the full Prescribing Information for ORKAMBI.

About Cystic Fibrosis

Cystic fibrosis is a rare, life-threatening 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, lead to CF by creating defective or too few CFTR proteins at the cell surface. The defective or missing CFTR protein results in poor flow of salt and water into or out of the cell in a number of organs, including 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 predicted age of survival for a person born today with CF is 41 years, but the median age of death is 27 years.

About Vertex

Vertex is a global biotechnology company that aims to discover, develop and commercialize innovative medicines so people with serious diseases can lead better lives. In addition to our clinical development programs focused on cystic fibrosis, Vertex has more than a dozen ongoing research programs aimed at other serious and life-threatening diseases.

Founded in 1989 in Cambridge, Mass., Vertex today has research and development sites and commercial offices in the United States, Europe, Canada and Australia. For seven years in a row, *Science* magazine has named Vertex one of its Top Employers in the life sciences. 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) and ORKAMBI (lumacaftor/ivacaftor) 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 from Dr. Chodakewitz and Dr. Ratjen and statements regarding Vertex's plans to submit a Marketing Authorization Application line extension to the EMA. 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 ORKAMBI or its other 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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