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## **Vertex Presents Long-Term Data Demonstrating that ORKAMBI® (lumacaftor/ivacaftor) and KALYDECO® (ivacaftor) Show the Potential to Modify the Progression of CF**

- 12 abstracts presented at 30<sup>th</sup> Annual North American Cystic Fibrosis Conference highlight data from Vertex's CF program

ORLANDO, Fla.--(BUSINESS WIRE)-- [Vertex Pharmaceuticals Incorporated](#) (Nasdaq: VRTX) today announced the presentation of long-term data demonstrating that ORKAMBI® (lumacaftor/ivacaftor) and KALYDECO® (ivacaftor) show the potential to modify the progression of cystic fibrosis (CF). The presentations given at the 30<sup>th</sup> Annual North American Cystic Fibrosis Conference (NACFC) include final data from the PROGRESS 96-week extension study of the pivotal 24-week Phase 3 studies of ORKAMBI in people ages 12 and older with two copies of the *F508del* mutation (TRAFFIC and TRANSPORT). Other highlights include an analysis of real-world outcomes in patients treated with KALYDECO using data from the United States Cystic Fibrosis Foundation Patient Registry (U.S. CFFPR) and United Kingdom Cystic Fibrosis Registry (U.K. CFR). Vertex will webcast an investor presentation from the conference at approximately 6:30 p.m. ET on Thursday, October 27 that will provide an overview of the company's progress to develop more medicines to treat the underlying cause of CF in all people with this disease. The webcast can be accessed live through Vertex's [website](#).

"The growing body of long-term data for KALYDECO and ORKAMBI indicates that treating the underlying cause of CF with CFTR modulators may modify the progression of this serious and life-shortening disease," said Jeffrey Chodakewitz, M.D., Executive Vice President and Chief Medical Officer at Vertex. "These data support our goal to develop increasingly effective combination regimens of CFTR modulators for all people with CF."

The 12 related abstracts presented at NACFC include data from studies of Vertex medicines and medicines in development. Highlights include:

### **Real-World Outcomes of Ivacaftor Treatment**

#### **Analysis of Real-World Outcomes in Patients with CF Treated with Ivacaftor from the 2014 U.S. and U.K. CF Registries**

Abstract #494, Workshop 23: Epidemiology of CF, Saturday, October 29, 10:56 a.m. to 11:06 a.m.

and

#### **Analysis of Disease Progression in Patients with CF Treated with Ivacaftor in the Real World Using Data From the U.K.CF Registry**

Abstract #495; Poster Session 1, Thursday, Oct. 27, 11:15 a.m. to 1:45 pm; Basic Science: Friday, Oct. 28, 4:00 p.m. to 6:00 p.m.

Interim data from the ongoing, five-year, post-approval observational safety study evaluating long-term outcomes in CF patients treated with ivacaftor showed the potential of ivacaftor to modify the progression of CF disease in a real-world setting. In total, these analyses included patients who had received ivacaftor for up to five years including 1,256 patients from the U.S. CFFPR who received an average of two years of treatment and 411 patients from the U.K. CFR who received an average of 1.3 years of treatment; and untreated patients with differing genotypes, including 6,200 from the U.S. CFFPR and 2,069 from the U.K. CFR. In the U.S. registry, the annual risks of death, transplantation, hospitalization and pulmonary exacerbation were each statistically significantly lower compared to the comparator cohort of matched patients who never received ivacaftor. Trends were similar in the U.K. registry, but the differences in the risk of death and transplantation were not statistically significant. No new safety concerns were identified, and the majority of the CF-related complications, such as CF-related diabetes and cultures positive for several microbial pathogens, were less common among ivacaftor-treated than untreated patients in both the U.S. and U.K. registries.

### **Evidence of Reduction in Annual Rate of FEV<sub>1</sub> Decline and Sustained Benefits with Lumacaftor and Ivacaftor in**

## **Patients with Cystic Fibrosis Homozygous for *F508del*-CFTR**

Abstract #180, Workshop 07: Clinical Advances in CF Research, Thursday, Oct. 27, 10:50 a.m. to 11:00 a.m. ET

An analysis of 96-week data from the PROGRESS extension study of the pivotal Phase 3 TRAFFIC and TRANSPORT studies of lumacaftor/ivacaftor in people ages 12 and older with two copies of the *F508del* mutation showed that lumacaftor/ivacaftor was generally well tolerated and had a safety profile consistent with that seen in TRAFFIC and TRANSPORT. In this 96-week safety extension study, all participants received one of two lumacaftor/ivacaftor combination regimens (400mg lumacaftor q12h in combination with 250mg ivacaftor q12h, or 600mg lumacaftor QD in combination with ivacaftor 250mg q12h). Mean lung function, a secondary endpoint of PROGRESS, was maintained above TRAFFIC/TRANSPORT baseline for up to 120 weeks.

An analysis of the rate of lung function decline was also conducted at week 96 of PROGRESS to compare the results for people who received the approved commercial dose of lumacaftor (400mg q12h) in combination with ivacaftor (250mg q12h) (n=455) to a propensity score matched cohort (n=1,588) of patients from the U.S. CFFPR. The analysis showed that lumacaftor/ivacaftor reduced the estimated annual rate of lung function decline by approximately 42 percent compared with matched controls. The annual rate of lung function decline among those receiving lumacaftor/ivacaftor was -1.33 percentage points compared to the matched control group, which had a rate of decline of -2.29 percentage points per year (p < 0.001).

The most common adverse events occurring in ≥20 percent of patients in either treatment group were pulmonary exacerbation, cough, sputum increased, hemoptysis, and dyspnea. Mean blood pressure increased from 113.4/68.7 mmHg at baseline of TRAFFIC/TRANSPORT to 118.0/72.8 mmHg at week 96 of PROGRESS in patients continuing lumacaftor 400 mg q12h/ivacaftor and increased from 113.2/68.6 mmHg at baseline of TRAFFIC/TRANSPORT to 119.1/73.5 mmHg at week 96 of PROGRESS in patients who transitioned from placebo to lumacaftor 400 mg q12h/ivacaftor.

"These data suggest that the benefits of lumacaftor/ivacaftor are sustained through 96 weeks and indicate that the medicine may modify the progression of CF lung disease by treating its underlying cause," said Michael W. Konstan, M.D., Vice Dean for Translational Research at Case Western Reserve University School of Medicine and Vice Chair for Clinical Research at University Hospitals Rainbow Babies & Children's Hospital who was the principal investigator of the study.

## **Safety, Tolerability, and Pharmacodynamics of Combination Lumacaftor/Ivacaftor Therapy in Patients Aged 6-11 years with CF Homozygous for the *F508del*-CFTR mutation**

Abstract 179; Workshop 07: Clinical Advances in CF Research, Thursday, Oct. 27, 10:35 a.m. to 10:45 a.m. ET

Final data from an open-label Phase 3 safety study that evaluated ORKAMBI in children with CF ages 6 through 11 who have two copies of the *F508del* mutation showed that lumacaftor/ivacaftor was generally well tolerated. The primary endpoint was safety. No new safety events were observed compared to older patients. Respiratory events (dyspnea, wheezing, respiration abnormal) were infrequent and not associated with any discontinuations. In the study, all children received a twice-daily fixed-dose combination of lumacaftor (200mg) and ivacaftor (250mg) for 24 weeks. These data supported the recent U.S. Food & Drug Administration approval of lumacaftor/ivacaftor in children ages 6 through 11 who have two copies of the *F508del* mutation.

## **Long-term Safety and Efficacy of Ivacaftor in Pediatric Patients Aged 2-5 years with CF and a *CFTR* Gating Mutation**

Abstract 177; Workshop 07: Clinical Advances in CF Research, Thursday, Oct. 27, 10:05 a.m. to 10:15 a.m.

Data from the KLIMB and KIWI studies of ivacaftor in children ages 2 through 5 with CF and a *CFTR* gating mutation showed that ivacaftor demonstrated a durable safety profile for a total of 108 weeks of continuous treatment. Sweat chloride reductions in the 24-week open label Phase 3 KIWI study were maintained through KLIMB, an 84-week open-label extension study. Age-normalized growth parameters were either maintained or improved from KIWI baseline through KLIMB. The most common adverse event of any grade was cough. Elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels > 3x the upper limit of normal (ULN) were reported in ten out of 33 patients. Of these ten, four had elevated ALT/AST levels of > 8x ULN in KIWI. Ivacaftor was maintained or resumed in all but one patient who discontinued and elevated ALT/AST levels resolved upon discontinuation.

## **About the Rate of Lung Function Decline Analysis**

PROGRESS is the 96-week extension study of TRAFFIC and TRANSPORT, the pivotal 24-week Phase 3 studies of ORKAMBI in people ages 12 and older with two copies of the *F508del* mutation. For the rate of lung function decline analysis, a propensity score approach was used to match patients from PROGRESS to patients from the U.S. CFFPR on

known predictors of lung function decline. Propensity scoring is a statistical matching technique used in observational research that attempts to balance the study groups to make them as similar as possible. The analysis compared 455 patients who received ORKAMBI for up to 96 weeks and observational data from the U.S. CFFPR on 1,588 control patients homozygous for the *F508del* mutation. Estimates of average annual rate of decline were based on lung function measurements spanning different lengths of time for different patients, with more patients contributing information about the rate of decline in the first year than in the second year.

## **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.

## **INDICATION AND IMPORTANT SAFETY INFORMATION FOR KALYDECO® (ivacaftor)**

KALYDECO (ivacaftor) is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients age 2 years and older who have one of the following mutations in their CF gene: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, *S549R*, or *R117H*. KALYDECO is not for use in people with CF due to other mutations in the CF gene. KALYDECO is not effective in patients with CF with two copies of the *F508del* mutation (*F508del/F508del*) in the CF gene. It is not known if KALYDECO is safe and effective in children under 2 years of age.

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

**Before taking KALYDECO, patients should tell their doctor if they:** have liver or kidney problems; drink grapefruit juice, or eat grapefruit or Seville oranges; are pregnant or plan to become pregnant because it is not known if KALYDECO will harm an unborn baby; and are breastfeeding or planning to breastfeed because it is not known if KALYDECO passes into breast milk.

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

KALYDECO can cause dizziness in some people who take it. Patients should not drive a car, use machinery, or do anything that needs them to be alert until they know how KALYDECO affects them. Patients should avoid food containing grapefruit or Seville oranges while taking KALYDECO.

**KALYDECO can cause serious side effects including:**

**High liver enzymes in the blood have been reported in patients receiving KALYDECO.** The patient's doctor will do blood tests to check their liver before starting KALYDECO, every 3 months during the first year of taking KALYDECO, and every year while taking KALYDECO. For patients who have had high liver enzymes in the past, the doctor may do blood tests to check the liver more often. 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 their skin or the white part of their eyes; loss of appetite; nausea or vomiting; or dark, amber-colored urine.

Abnormality of the eye lens (cataract) has been noted in some children and adolescents receiving KALYDECO. The patient's doctor should perform eye examinations prior to and during treatment with KALYDECO to look for cataracts. The most common side effects include headache; upper respiratory tract infection (common cold), which includes sore throat, nasal or sinus congestion, and runny nose; stomach (abdominal) pain; diarrhea; rash; nausea; and dizziness.

These are not all the possible side effects of KALYDECO. **Please click [here](#) to see the full Prescribing Information for KALYDECO (ivacaftor).**

## 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 six 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](http://www.vrtx.com).

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## **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. Konstan. 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, KALYDECO 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](http://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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## **Vertex Pharmaceuticals Incorporated**

### **Investors:**

Michael Partridge, 617-341-6108

or

Eric Rojas, 617-961-7205

or

Zach Barber, 617-341-6470

or

**Media:** [mediainfo@vrtx.com](mailto:mediainfo@vrtx.com)

North America:

Chris Stamm, +1 617-341-6992

or

Europe & Australia:

Megan Goulart, +44 20 3204 5275

Source: Vertex Pharmaceuticals Incorporated

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