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# Vertex Announces Significant Progress in Its Development Efforts to Treat the Cause of Cystic Fibrosis in the Vast Majority of People with the Disease

*-Two next-generation correctors to enter clinical development in November; studies of a triple combination of a next-generation corrector with VX-661/ivacaftor planned for 2016 in people with CF-*

*-Treating the underlying cause of CF with ORKAMBI® (lumacaftor/ivacaftor) or KALYDECO® (ivacaftor) highlighted as part of multiple data presentations at North American CF Conference-*

PHOENIX--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced significant progress in its development efforts to treat the underlying cause of cystic fibrosis (CF) for the vast majority of people with the disease. These updates were made in conjunction with the 29th Annual North American Cystic Fibrosis Conference (NACFC), which begins today in Phoenix. Vertex will webcast an investor presentation from the conference at approximately 6:15 p.m. MST (9:15 p.m. EDT) on Friday, October 9. The webcast can be accessed live through Vertex's website.

"With continued expansion in the number of people eligible for KALYDECO, the recent FDA approval of ORKAMBI in the U.S. and the advancement of two next-generation correctors into clinical development, we are making significant progress toward our goal of treating the vast majority of people with CF," said Jeffrey Chodakewitz, M.D., Executive Vice President and Chief Medical Officer at Vertex. "We are conducting studies with our investigational combination regimens in groups of CF patients with mutations that represent approximately 90 percent of all people with CF. While there is much work still to be done, we believe we are on the right path to further enhance the treatment of CF in the years ahead."

More than 15 abstracts related to Vertex's CF development program were accepted for presentation at NACFC. Vertex today provided the following updates to its development program in CF and highlighted select presentations from the conference:

## Two Next-Generation Correctors To Enter Clinical Development

Vertex today announced that it is advancing two next-generation correctors from its research program into clinical development. Known as VX-152 and VX-440, these next-generation correctors will be evaluated alone and in combination with VX-661/ivacaftor in Phase 1 studies in healthy volunteers beginning in November 2015. Pending results of these studies, Vertex plans to initiate Phase 2 studies in people with CF evaluating VX-440 or VX-152 in combination with VX-661/ivacaftor in the second half of 2016. The studies of a triple combination (VX-152/VX-661/ivacaftor and VX-440/VX-661/ivacaftor) planned for the second half of 2016 are expected to enroll people with CF who have two copies of the *F508del* mutation and people who have one copy of the *F508del* mutation and a second mutation that results in minimal CFTR function. VX-152 and VX-440 are designed to further improve processing and trafficking of the CFTR protein to the cell surface, beyond that observed with a single corrector combined with ivacaftor, which may enable increased CFTR chloride transport, a measure of the function of the CFTR protein at the cell surface.

In human bronchial epithelial (HBE) cells with two copies of the *F508del* mutation and in HBE cells with one copy of the *F508del* mutation and one copy of a mutation known to result in minimal CFTR function, the triple combinations (VX-152/VX-661/ivacaftor and VX-440/VX-661/ivacaftor) resulted in chloride transport (percent of normal) that was approximately three-fold greater than the use of the lumacaftor/ivacaftor combination in these cells. A significant increase in cilia beat frequency was also observed with triple combination therapy as compared to the use of the lumacaftor/ivacaftor combination in these cells. These *in vitro* data suggest that a triple combination of a next-generation corrector with VX-661/ivacaftor may improve CFTR function in cells with two copies of the *F508del* mutation and cells with one copy of the *F508del* mutation and one copy of a mutation known to result in minimal CFTR function.

## KALYDECO® (ivacaftor)

***Supplemental New Drug Application in Residual Function Mutations:*** On October 7, Vertex announced that its supplemental New Drug Application for the use of KALYDECO in people ages two and older with one of 23 residual function mutations was accepted for review by the FDA. The FDA granted Vertex's request for Priority Review of this sNDA, and a target review date of February 6, 2016 was set under the Prescription Drug User Fee Act (PDUFA) for the FDA's decision on the sNDA. More than 1,500 people with CF in the U.S. have the mutations represented in the sNDA.

***Study in Children Less Than Two Years of Age:*** As CF-related complications can emerge early in life, Vertex plans to conduct a clinical study of KALYDECO in children less than two years of age to evaluate the effect of KALYDECO on markers of CF disease in young children. The study will utilize a weight-based dose of KALYDECO granules that can be mixed in soft foods or liquids. The study is expected to begin in the first quarter of 2016.

***Positive Opinions from European Union CHMP:*** On September 25, Vertex announced that the EU Committee for Medicinal Products for Human Use (CHMP) issued positive opinions recommending KALYDECO for use in children ages 2 to 5 with CF who have one of nine gating mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene and in people with CF ages 18 and older who have the *R117H* mutation. In Europe, approximately 125 children with CF ages 2 to 5 have one of the nine gating mutations included in the positive opinion, and approximately 250 adults have the *R117H* mutation.

***Select NACFC Presentations:***

- ***Long-Term Safety Data of Ivacaftor Treatment:*** Interim data from an ongoing 5-year observational study evaluating the long-term outcomes in people treated with ivacaftor will be presented at NACFC for the first time. In this analysis, which is based on data from the 2013 CF Foundation Patient Registry, 999 patients were treated with ivacaftor for an average duration of treatment of 1.4 years. As of 2013, the annual risk of death, organ transplantation, hospitalization due to any reason and frequency of pulmonary exacerbations were all significantly lower in the ivacaftor group compared to matched controls from the CF Foundation Patient Registry. No CF-related complications were significantly more common in the ivacaftor group. These data will be presented as part of a poster titled "Ivacaftor Long-term Safety Study: Analysis of 2013 US CF Foundation Patient Registry Data."
- ***Correlation of Rate of Lung Function Decline with Acute Improvements in Lung Function in STRIVE, ENVISION and PERSIST Studies:*** A post-hoc analysis of the STRIVE, ENVISION and PERSIST studies of ivacaftor evaluating whether there was any correlation between acute improvement in lung function (percent predicted forced expiratory volume in one second; $ppFEV_1$) and the long-term rate of lung function decline will be presented at NACFC as part of a Workshop Session. The results showed that there were no significant correlations between rate of lung function decline and baseline $ppFEV_1$ values, absolute acute improvement in $ppFEV_1$, or relative acute improvement in $ppFEV_1$. These data will be presented as part of a poster titled "Improved Rate of Decline in Percent Predicted $FEV_1$ is Not Associated With Acute Improvement in Percent Predicted $FEV_1$ in Patients With Cystic Fibrosis Treated With Ivacaftor" that will be discussed as part of Poster Discussion/Workshop Session 24, New Therapies.
- ***Changes in Height with Ivacaftor Treatment:*** A post-hoc analysis of the ENVISON study of ivacaftor in children ages 6 to 11 years with the *G551D* mutation evaluated the effect of ivacaftor on linear growth (height) and other growth measures and will be presented at NACFC for the first time. The results showed that ivacaftor treatment resulted in an improvement in multiple growth parameters, including linear growth, in children with CF. These data will be presented as part of a poster titled "Ivacaftor Improves Linear Growth in *G551D* Cystic Fibrosis Children: Results of a Multicenter, Placebo-Controlled Study" and will also be presented as part of Workshop Session 10, Nutrition Research.

**ORKAMBI® (lumacaftor/ivacaftor)**

***Positive Opinion from EU CHMP for ORKAMBI:*** On September 25, Vertex announced that the EU CHMP issued a positive opinion recommending ORKAMBI for use in people ages 12 and older with two copies of the *F508del* mutation. In Europe, approximately 12,000 people with CF ages 12 and older have two copies of this mutation.

***Ongoing Phase 3 Studies in Children Ages 6 to 11:*** Vertex is currently conducting two Phase 3 clinical studies of lumacaftor/ivacaftor in children 6 to 11 years of age. The first study is evaluating lumacaftor/ivacaftor in approximately 50 children to support the potential FDA approval in children ages 6 to 11. The primary endpoint of this six-month study is safety. Vertex plans to submit an sNDA to the FDA in the first half of 2016, pending data from this study. To support approval in the European Union, a six-month Phase 3 efficacy study is ongoing to evaluate lumacaftor/ivacaftor in approximately 200 children. The primary endpoint of the second study is the absolute change in lung clearance index.

***Select NACFC Presentations:***

- ***Correlation of Pulmonary Exacerbations with Acute Improvements in Lung Function in TRAFFIC and TRANSPORT Studies:*** Data from a post-hoc analysis evaluating the correlation of acute lung function improvements to reductions in pulmonary exacerbations in the Phase 3 TRAFFIC and TRANSPORT studies showed that treatment with lumacaftor/ivacaftor resulted in a reduction in the frequency of pulmonary exacerbations regardless of the acute improvement in lung function at Day 15 in the study. These data will be presented for the first time at NACFC in a poster titled "Association Between Changes in Percent Predicted $FEV_1$ and Incidence of Pulmonary Exacerbations, Including Those Requiring Hospitalization and/or IV Antibiotics, in Patients With CF Treated With Lumacaftor in Combination With Ivacaftor."

- ***Efficacy and Safety of Lumacaftor/Ivacaftor Across Sub-Groups in TRAFFIC and TRANSPORT Studies:*** A pre-specified pooled analysis that evaluated whether baseline lung function was predictive of the efficacy and safety of lumacaftor/ivacaftor treatment will be presented at NACFC for the first time. In this analysis, patients were stratified based on their screening and study baseline lung function values. The results showed that the efficacy and safety of lumacaftor/ivacaftor were generally similar across lung function subgroups. These data will be presented as part of a poster titled "Efficacy and Safety of Lumacaftor/Ivacaftor Combination Therapy in Patients With CF Homozygous for F508del-CFTR by $FEV_1$ Subgroups."

**VX-661 in Combination with Ivacaftor**

Four Phase 3 studies of the investigational combination of VX-661 and ivacaftor are ongoing in multiple different groups of people with CF who have at least one copy of the *F508del* mutation. The studies are evaluating VX-661 dosed as 100 mg once daily (QD) in combination with ivacaftor dosed as 150 mg every 12 hours (q12h). These studies are enrolling people with CF with the following mutations:

- Two Copies of the *F508del* Mutation
- One Copy of the *F508del* Mutation and a Second Mutation that Results in a Gating Defect in the CFTR Protein
- One Copy of the *F508del* Mutation and a Second Mutation That Results in Residual CFTR Function
- One Copy of the *F508del* Mutation and A Second Mutation That Results in Minimal CFTR Function

Together, these studies are expected to enroll more than 1,000 people with CF, and enrollment in each of these studies is ongoing. Vertex expects to complete enrollment in the first three studies, and in the first part of the study in people with a mutation that results in minimal CFTR function, in mid-2016.

**Studies of the ENaC Inhibitor VX-371**

In June 2015, Vertex and Parion Sciences entered into a collaboration to develop investigational epithelial sodium channel (ENaC) inhibitors for the potential treatment of cystic fibrosis (CF) and other pulmonary diseases. Parion is currently conducting an exploratory Phase 2a study (known as the CLEAN-CF study) of inhaled VX-371 (P-1037), compared to treatment with VX-371 with hypertonic saline, in approximately 120 people with CF. The study is enrolling people with a confirmed diagnosis of CF and any *CFTR* mutation. Additionally, Vertex plans to conduct a placebo-controlled Phase 2a study to evaluate VX-371 in patients taking lumacaftor/ivacaftor, both with and without the addition of hypertonic saline, who have two copies of the *F508del* mutation. This Phase 2a study is expected to begin in early 2016.

Preclinical evaluation in human bronchial epithelial cells from people with CF who have two copies of the *F508del* mutation showed that the addition of investigational VX-371 to lumacaftor/ivacaftor resulted in an additional increase in both airway surface liquid and cilia beat frequency compared to baseline and to the use of VX-371 or lumacaftor/ivacaftor alone. Improvements in airway surface liquid height and cilia beat frequency are measures of increased hydration of the cell surface.

Preclinical and clinical data for VX-371 will be presented by Parion at NACFC and support the ongoing Phase 2 evaluation of VX-371.

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

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.

**IMPORTANT SAFETY INFORMATION**

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 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. A patient 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. 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.

Please click here to see the full Prescribing Information for KALYDECO (ivacaftor).

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

ORKAMBI is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients age 12 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 12 years of age.

**IMPORTANT SAFETY INFORMATION**

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 or have kidney problems; are using birth control (hormonal contraceptives, including oral, injectable, transdermal or implantable forms) because hormonal contraceptives should not be used as a method of birth control when taking ORKAMBI; are pregnant or plan to become pregnant because it is unknown if ORKAMBI will harm the unborn baby; are breastfeeding or planning to breastfeed as 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, a patient 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. A patient 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.

Abnormality of the eye lens (cataract) has been noted in some children and adolescents receiving ivacaftor, a component of ORKAMBI. 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 five 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 1998 as part of a collaboration with CFFT, the nonprofit drug discovery and development affiliate of the Cystic Fibrosis Foundation. KALYDECO and ORKAMBI 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. Chodakewitz's statements in the second paragraph of the press release, the expectation that VX-152 and VX-440 will be evaluated in Phase 1 studies beginning in November 2015 and Vertex's plans regarding initiating Phase 2 studies of VX-440 or VX-152 in the second half of 2016, the expected timing and clinical study designs for Vertex's ongoing and future clinical studies, including the (i) clinical study of KALYDECO in children less than two years of age, (ii) Phase 3 clinical studies of lumacaftor/ivacaftor in children 6 to 11 years of age, (iii) Phase 3 program of VX-661 in combination with ivacaftor, (iv) Phase 2a clinical studies of VX-371 (P-1037) and (v) next-generation corrector program, including clinical studies involving VX-152 and VX-440, and information related to sNDA for KALYDECO in patients ages 2 and older who have one of 23 residual function mutations. While Vertex believes the forward-looking statements contained in this press release are accurate, 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 *in vitro* responses may not be predictive of clinical results, that regulatory authorities may not approve, or approve on a timely basis, the sNDA for KALYDECO for patients with one of 23 residual function mutations, 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 the 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.

**Investor Webcast**

Vertex will webcast an investor presentation from NACFC at approximately 6:15 p.m. MST (9:15 p.m. EDT) on Friday, October 9. A link to the webcast can be accessed through Vertex's website at www.vrtx.com in the "Investors" section under "Events and Presentations." To ensure a timely connection, it is recommended that users register at least 15 minutes prior to the scheduled

webcast. An archived webcast will be available on the company's website.

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