June 12, 2014

Vertex Announces Presentation of New KALYDECO™ (ivacaftor) Data at European Cystic Fibrosis Society Conference

-New data showed that KALYDECO reduced the loss of lung function by half over 3 years in people with CF who have the G551D mutation compared to similar untreated patients-

-New data from rollover study of ivacaftor in people with the R117H mutation support earlier results from Phase 3 study that demonstrated lung function improvements in patients ages 18 and older-

-New data showed that previously reported lung function improvements in Phase 3 ivacaftor study in people with certain non-G551D gating mutations were maintained through 24 weeks-

GOTHENBURG, Sweden--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced the presentation of new KALYDECO™ (ivacaftor) data at the 37th European Cystic Fibrosis Society (ECFS) Conference, June 11-14, 2014, in Gothenburg, Sweden. New data from an analysis of Phase 3 and long-term extension studies in people with cystic fibrosis (CF) who have the G551D mutation showed that treatment with KALYDECO reduced the annual loss of lung function by half over three years compared to similar untreated CF patients. In addition, the first data from a rollover study following the Phase 3 KONDUCT study in people with the R117H mutation confirmed earlier results that demonstrated lung function improvements in people ages 18 and older. New data were also presented for the first time from the second part of the Phase 3 KONNECTION study in people with certain non-G551D gating mutations and showed that previously reported lung function improvements were maintained through 24 weeks of treatment.

"People with cystic fibrosis experience significant and progressive loss of lung function during their lives. This decline in lung function is the primary cause of death in people with CF, and more rapid loss of lung function is associated with earlier death," said Jeffrey Chodakewitz, M.D., Senior Vice President and Chief Medical Officer at Vertex. "Not only does KALYDECO lead to significant initial improvements, but these new long-term data showed that it also appeared to modify the rate of lung function decline, reducing the loss of lung function in people with the G551D mutation. These findings, together with new data from studies in people with the R117H mutation and certain non-G551D gating mutations, show our continued progress in evaluating the benefits of this medicine across different groups of patients and also show that our approach to treating the underlying cause of CF can provide benefits for people with this rare and devastating disease."

The effect of ivacaftor on the rate of lung function decline in CF patients with a G551D-CFTR mutation *(ECFS Abstract WS3.1, Thursday at 15.00 CEST)*

Progressive loss of lung function, due to chronic lung disease, is the primary cause of death for people with cystic fibrosis.

New data from an analysis of the Phase 3 STRIVE and ENVISION studies, and from patients who rolled over into the long-term extension study PERSIST, were presented at the conference and showed that treatment with KALYDECO in people with CF ages 6 and older with the G551D mutation appeared to modify the rate of lung function decline, reducing the annual loss of lung function by half over three years. The annual rate of decline among those receiving KALYDECO was 0.81 FEV_1 percentage points compared to an untreated group of people matched on clinical criteria with two copies of the F508del mutation, whose annual rate of decline was 1.73 percentage points (p=0.02).

This analysis was conducted by comparing the change in lung function in people who received KALYDECO in the Phase 3 STRIVE, ENVISION and PERSIST trials (n=189) with lung function changes in a matched control group derived from the U.S. Cystic Fibrosis Foundation Patient Registry who had two copies of the F508del mutation and similar disease severity (n=886). Historical data have previously shown a similar rate of lung function decline among people with two copies of the F508del mutation and those with the G551D mutation.

KONDUCT Study

Ivacaftor treatment in patients with cystic fibrosis who have an R117H-CFTR mutation, the KONDUCT Study *(ECFS Abstract WS23.6, Friday at 18.15 CEST)*

Vertex today announced interim results from the open-label rollover study of ivacaftor in people with CF ages 6 and older who have the R117H mutation. Sixty-five of the 67 eligible people who completed the KONDUCT study continued into this rollover study. As previously announced, the KONDUCT study did not meet its primary endpoint of absolute change from baseline in FEV_1 (forced expiratory volume in one second) through 24 weeks in the overall study population. However, a pre-specified subset analysis showed that the mean absolute improvement in lung function compared to placebo (treatment difference) for patients ages 18 and older was 5.0 (p=0.01) percentage points, which corresponded to a mean relative improvement of 9.1 (p=0.008) percent. Statistically significant improvements in key secondary endpoints, including sweat chloride and patient-reported respiratory symptoms as measured by the respiratory domain of the Cystic Fibrosis Questionnaire Revised (CFQ-R), were also observed regardless of age.

In the rollover study, all patients received ivacaftor after a washout period of at least three weeks following the KONDUCT study. The interim data announced today were obtained following a pre-planned analysis conducted after all patients reached the 12-week timepoint in the rollover study. After the first 12 weeks of the rollover study, the mean absolute improvement from baseline in lung function (percent predicted FEV_1) was 5.5 percentage points ($p < 0.0001$) among all patients (n=62; intent-to-treat analysis). For patients ages 18 and older (n=46), the mean absolute improvement in lung function was 5.1 percentage points ($p < 0.0001$). For patients ages 6 to 11 (n=15), the mean absolute improvement in lung function was 6.5 percentage points; the decline in FEV_1 observed in the KONDUCT study for patients ages 6 to 11 who received ivacaftor was not observed in the rollover study. Similar to the KONDUCT study, treatment with ivacaftor, regardless of age, resulted in decreases in sweat chloride and improvements in CFQ-R.

In the 24-week KONDUCT study and through 12 weeks in the rollover study, the safety and tolerability results were consistent with those observed in prior Phase 3 studies of ivacaftor monotherapy in people with CF who have the G551D and other gating mutations. In KONDUCT, the most commonly observed adverse events in those who received ivacaftor were infective pulmonary exacerbation, cough and headache, which occurred with similar frequency compared to those who received placebo. Serious adverse events occurred in 17 percent of patients who received placebo versus 12 percent of patients who received ivacaftor. In the rollover study, the most common serious adverse events were infective pulmonary exacerbations.

Based on these data, Vertex plans to submit a supplemental New Drug Application (sNDA) in the U.S. and a marketing authorization application (MAA) variation in Europe for people ages 18 and older who have the R117H mutation. The sNDA submission is planned for mid-2014, followed by the MAA variation submission in the second half of 2014.

KONNECTION Study

The effect of ivacaftor, a CFTR potentiator, in patients with cystic fibrosis and a non-G551D-CFTR gating mutation, the KONNECTION Study *(ECFS Abstract WS1.1, Thursday at 15.00 CEST)*

Results from the second part of the Phase 3 KONNECTION study of ivacaftor in people with CF ages 6 and older who have at least one copy of certain non-G551D gating mutations (G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D and G970R) were presented for the first time at the conference. These data showed that the previously reported improvements in lung function, sweat chloride, BMI and CFQ-R scores after eight weeks of treatment (Part 1) were maintained through 24 weeks. The mean absolute improvement, from baseline, in lung function, as measured by FEV_1, through 24 weeks of treatment was 13.5 percentage points (n=18). The safety and tolerability results observed through 24 weeks of treatment were consistent with those observed during the eight-week first part of the study, reported in July 2013, as well as with prior Phase 3 studies of ivacaftor in people ages 6 and older with the G551D mutation.

The primary endpoint in the second part of the study was absolute change from baseline in lung function, as measured by FEV_1, through 24 consecutive weeks of treatment for those who received ivacaftor in the second sequence of Part 1 of the study (n=18), which included eight weeks of ivacaftor treatment in Part 1 of the study plus 16 additional weeks in Part 2 of the study.

Hyperpolarized Helium-3 MRI Study

The effect of ivacaftor treatment on lung ventilation defects, as measured by hyperpolarized helium-3 MRI, on patients with cystic fibrosis and a G551D-CFTR mutation *(ECFS Abstract WS3.2, Thursday at 15.15 CEST)*

CF-related lung disease is known to start before it is detectable by deterioration in FEV_1. Once FEV_1 has fallen below normal (90 percent predicted), structural damage may have already occurred, much of which can be irreversible. Using a new imaging technology, hyperpolarized helium-3 MRI (3He-MRI) that is more sensitive to early- and mild-stage lung disease and gradual disease progression, this study showed that treatment with KALYDECO alleviated airway obstructions in the lung and benefited people with normal FEV_1.

About KALYDECO™ (ivacaftor)

KALYDECO (ivacaftor) is the first medicine to treat the underlying cause of CF in people with specific mutations in the *CFTR* gene. Known as a CFTR potentiator, KALYDECO is an oral medicine that aims to help the CFTR protein function more normally once it reaches the cell surface, to help hydrate and clear mucus from the airways. KALYDECO (150mg, q12h) was first approved by the U.S. Food and Drug Administration in January 2012 for use in people with CF ages 6 and older who have at least one copy of the G551D mutation and in February 2014 for use in people with CF ages 6 and older who have the following additional CFTR mutations: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P and G1349D. In Canada, KALYDECO was first approved in November 2012 for use in people with CF ages 6 and older who have at least one copy of the G551D mutation and in June 2014 for use in people with CF ages 6 and older who have the following additional CFTR mutations: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D and G970R.

KALYDECO was approved by the European Medicines Agency in July 2012 and by the Therapeutic Goods Administration in Australia in July 2013 for use in people with CF ages 6 and older who have at least one copy of the G551D mutation in the *CFTR* gene.

Vertex retains worldwide rights to develop and commercialize KALYDECO.

INDICATION AND IMPORTANT SAFETY INFORMATION FOR KALYDECO™ (ivacaftor)

Ivacaftor (150 mg tablets) is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a *G551D* mutation in the *CFTR* gene.

In the United States, ivacaftor is also indicated for the treatment of CF in patients age 6 and older who have one of the following mutations in the *CFTR* gene: *G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R*. In Canada, ivacaftor is indicated for these same mutations and additionally for *G970R*.

Ivacaftor is not effective in patients with CF with 2 copies of the *F508del* mutation (*F508del/F508del*) in the *CFTR* gene. The safety and efficacy of ivacaftor in children with CF younger than 6 years of age have not been established.

Elevated liver enzymes (transaminases; ALT and AST) have been reported in patients receiving ivacaftor. It is recommended that ALT and AST be assessed prior to initiating ivacaftor, every 3 months during the first year of treatment, and annually thereafter. Patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the upper limit of normal. Following resolution of transaminase elevations, consider the benefits and risks of resuming ivacaftor dosing.

Use of ivacaftor with medicines that are strong CYP3A inducers, such as the antibiotics rifampin and rifabutin; seizure medications (phenobarbital, carbamazepine, or phenytoin); and the herbal supplement St. John's Wort, substantially decreases exposure of ivacaftor and may diminish effectiveness. Therefore, co-administration is not recommended.

The dose of ivacaftor must be adjusted when used concomitantly with strong and moderate CYP3A inhibitors or when used in patients with moderate or severe hepatic disease.

Ivacaftor can cause serious adverse reactions including abdominal pain and high liver enzymes in the blood. The most common side effects associated with ivacaftor include headache; upper respiratory tract infection (the common cold), including sore throat, nasal or sinus congestion, and runny nose; stomach (abdominal) pain; diarrhea; rash; and dizziness. These are not all the possible side effects of ivacaftor. A list of the adverse reactions can be found in the product labeling for each country where ivacaftor is approved. Patients should tell their healthcare providers about any side effect that bothers them or does not go away.

Please see KALYDECO U.S. Prescribing Information, EU Summary of Product Characteristics, Canadian Product Monograph, Australian Consumer Medicine Information and Product Information, Swiss Prescribing Information and Patient Information, and the New Zealand Datasheet and Consumer Medicine Information.

About Cystic Fibrosis

Cystic fibrosis is a rare, life-shortening genetic disease affecting approximately 75,000 people in North America, Europe and Australia. Today, the median predicted age of survival for a person with CF is between 34 and 47 years, but the median age of death remains in the mid-20s.

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 more than 1,900 known mutations in

the *CFTR* gene. Some of these mutations, which can be determined by a genetic, or genotyping test, lead to CF by creating non-working or too few CFTR protein at the cell surface. The defective function or absence of CFTR proteins in people with CF results in poor flow of salt and water into and 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.

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. This collaboration was expanded to support the accelerated discovery and development of Vertex's CFTR modulators.

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 four 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.

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, and the information provided regarding (i) Vertex's plans to submit an sNDA in the U.S. and an MAA variation in Europe for people with CF ages 18 and older who have the R117H mutation and (ii) the data that Vertex expects will be presented at the 37th European Cystic Fibrosis Society (ECFS) Conference in Gothenburg, Sweden, June 11 to 14, 2014. 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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Source: Vertex Pharmaceuticals Incorporated

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