November 3, 2017

Vertex Announces Presentations of Data at North American Cystic Fibrosis Conference that Demonstrate Important Progress Toward Goal of Helping All People with CF

- Data from ongoing extension study of ORKAMBI® (lumacaftor/ivacaftor) in children ages 6-11 and real-world KALYDECO® (ivacaftor) data demonstrate long-term safety and other benefits of these medicines -

- New data from ongoing extension study of tezacaftor/ivacaftor combination demonstrate sustained benefits up to 48 total weeks of treatment -

- First presentation of previously announced early data from Phase 1 and Phase 2 studies of three different triple combination regimens -

INDIANAPOLIS--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq:VRTX) today announced presentations of data at the Annual North American Cystic Fibrosis Conference (NACFC), November 2 to 4, 2017, in Indianapolis, from across the company's portfolio of cystic fibrosis (CF) medicines and medicines in development that demonstrate important progress toward the company's goal of helping all people with CF. Key presentations highlight the acute and long-term benefits of CFTR modulation, including data from an ongoing extension study of ORKAMBI® (lumacaftor/ivacaftor) showing that improvements in lung function and other measures of disease were maintained through 48 weeks in children with CF ages 6 to 11 who have two copies of the *F508del* mutation, and real-world data demonstrating the impact of KALYDECO® (ivacaftor) across multiple CF measures in slowing disease progression. Also being presented at the Conference are new data from an ongoing extension study of the tezacaftor/ivacaftor combination demonstrating sustained benefits for up to 48 total weeks of treatment, and the first presentation of previously announced data from Phase 1 and Phase 2 studies of three different triple combination regimens.

"The breadth of data presented at this meeting demonstrate significant progress toward our key goals of bringing disease-modifying medicines to all people with CF and increasing the benefits for patients on our current medicines," said Jeffrey Chodakewitz, M.D., Executive Vice President and Chief Medical Officer at Vertex. "We also know that many people with CF are still waiting for a medicine to treat the cause of their disease and we are continuing our efforts to develop additional new medicines, such as triple combination regimens, for these people with a sense of urgency."

ORKAMBI in Children Ages 6 to 11

"Safety and Efficacy of Lumacaftor/Ivacaftor (LUM/IVA) in Patients aged ≥6 years with CF Homozygous for F508del-CFTR (Phase 3 Extension Study)." Poster 278.

Two hundred and forty children ages 6 to 11 who have two copies of the *F508del* mutation and who completed 24 weeks of treatment in either the Phase 3 randomized, double-blind, placebo-controlled ORKAMBI study (designed to support approval in the EU) or the open-label Phase 3 ORKAMBI safety study (designed to support approval in the U.S.) entered a Phase 3 rollover study to receive ORKAMBI for an additional 96 weeks. A pre-planned interim analysis was conducted once all participants completed 24 weeks in the rollover study for a total of 48 total weeks of ORKAMBI treatment (48 weeks for those who received ORKAMBI in the placebo-controlled study or in the open-label study; 24 weeks for those who received placebo in the placebo-controlled study).

This analysis showed that the improvements over baseline in lung function (measured by the absolute change in lung clearance index, or $LCI_{2.5}$), sweat chloride and body mass index (BMI) were maintained through 48 weeks of treatment. In addition, the pattern and magnitude of response observed after the initiation of ORKAMBI in children who previously received placebo were similar to those seen among children who received ORKAMBI in the initial studies.

Safety data from this interim analysis were similar to those observed in previous Phase 3 studies in children ages 6 to 11. Most adverse events were mild or moderate. Six patients discontinued treatment due to adverse events (3 due liver enzyme elevations, 1 due to autoimmune hepatitis, 1 due to a gastrointestinal disorder and 1 due to urticaria (hives)). The most common adverse events (≥15%) were cough, infective pulmonary exacerbation, pyrexia (fever), nasal congestion, headache and upper respiratory tract infection. Serious adverse events were reported in 40 patients (17%). Predefined respiratory events were observed more frequently in those who previously received placebo compared to those who

continued ORKAMBI treatment (19.8% vs 8.4%); all were mild or moderate, and none led to treatment discontinuation. Six patients (2.5%) experienced elevated liver enzymes of greater than eight times the upper limit of normal. Of the three patients who discontinued treatment due to elevated liver enzymes, all levels returned to baseline after stopping treatment.

"Cystic fibrosis is a progressive disease where the damage begins at birth," said Mark Chilvers, M.D., lead investigator for the rollover study, BC Children's Hospital, Clinical Associate Professor, Division of Respiratory Medicine, Department of Pediatrics, Faculty of Medicine, University of British Columbia. "Because of this, it is critical to begin treating the disease as early as possible. These data are important because they demonstrate that in children as young as 6 years of age, ORKAMBI is well tolerated and that the respiratory and nutritional changes are sustained over time."

"Effect of Lumacaftor/Ivacaftor on Total, Bronchiectasis, and Air Trapping Computed Tomography (CT) Scores in Children Homozygous for F508del-CFTR: Exploratory Imaging Substudy." Poster 197. Oral presentation during Workshop W18--NT: Innovative Approaches to CF Therapy.

"Feasibility of Ultrashort Echo Time (UTE) MRI to Evaluate the Effect of Lumacaftor/Ivacaftor Therapy in Children with Cystic Fibrosis (CF) Homozygous for F508del." Poster 266.

CF-related lung disease is known to start before it is detectable by a decrease in lung function as measured by percent predicted forced expiratory volume in one second, or ppFEV$_1$. Once ppFEV$_1$ has fallen below normal, structural lung damage may have already occurred; much of this can be irreversible.

This exploratory sub-study was conducted in 19 children with CF ages 6 to 11 who have two copies of the *F508del* mutation and who participated in the Phase 3 ORKAMBI study designed to support EU approval (n=206). An exploratory analysis of CT and MRI scans was used to evaluate treatment effects in children with CF with mild lung disease. In the 24-week exploratory analysis, treatment with ORKAMBI showed positive trends toward improvement in Total Brody Score, which is a system that evaluates the extent and severity of structural lung damage. These results demonstrate the potential utility of CT and MRI for monitoring the treatment effects of CFTR modulators.

KALYDECO Real-World Outcomes

"Real-World Outcomes in Patients with CF Treated with Ivacaftor: 2015 US and UK CF Registry Analyses." Poster 496.

"Disease Progression in Patients with CF Treated with Ivacaftor: Analyses of Real-World Data from the US and UK CF Registries." Poster 497.

Interim data collected through 2015 from the ongoing, five-year, post-approval observational safety study evaluating long-term outcomes in CF patients on KALYDECO continue to support that treating the underlying cause of CF has the potential to modify the course of disease in a real-world setting.

In both the U.S. and UK registries, patients who received KALYDECO in 2015 had lower risk of death, transplantation, hospitalizations and pulmonary exacerbations compared to patients who were matched on age, gender and genotype class who did not receive KALYDECO. In addition, select CF-related complications were less common in patients who received KALYDECO. Patients who received KALYDECO from year one of commercial availability had consistently better preserved lung function and improved nutritional measures compared to matched untreated patients. No new safety concerns were identified. These data further add to the growing body of evidence showing disease modification by CFTR modulator treatment.

In total, the analyses included 1,727 patients from the U.S. Cystic Fibrosis Foundation Patient Registry (CFFPR) and 432 patients from the U.K. Cystic Fibrosis Registry (CFR) who had received ivacaftor in 2015.

EVOLVE, EXPAND and EXTEND Phase 3 Studies of Tezacaftor/Ivacaftor

"Efficacy and Safety of Tezacaftor/Ivacaftor in Patients aged ≥12 with CF Homozygous for F508del-CFTR: A Randomized Placebo (PBO) - Controlled Phase 3 Trial." Oral presentation S14.1 during Symposium S14--NT: CF Interventions Advancing Through the Clinical Testing Phase.

"Efficacy and Safety of Tezacaftor/Ivacaftor in Patients aged ≥12 with CF Heterozygous for F508DEL and a Residual Function Mutation: A randomized, double-blind, Placebo-Controlled, Crossover Phase 3 Study." Oral presentation S14.2 during Symposium S14--NT: CF Interventions Advancing Through the Clinical Testing Phase.

The first data from the ongoing 96-week EXTEND Phase 3 rollover study of the tezacaftor/ivacaftor combination were presented during oral presentations at NACFC. Patients who completed the Phase 3 EVOLVE and EXPAND

tezacaftor/ivacaftor studies were eligible to enter an open-label Phase 3 rollover study, called EXTEND, to receive tezacaftor/ivacaftor for 96 weeks. This preplanned interim analysis was conducted when approximately 70 percent of patients from the EVOLVE study reached 24 weeks in the EXTEND study and when approximately 70 percent of patients from the EXPAND study reached 16 weeks in the EXTEND study.

This analysis showed that the initial improvements in lung function (measured by the absolute change in $ppFEV_1$) observed in the Phase 3 EVOLVE and EXPAND studies were sustained for up to 48 total weeks of treatment (24 weeks in EVOLVE + 24 weeks in EXTEND, or 8 weeks in EXPAND + 16 weeks in EXTEND). Safety data from this interim analysis showed that tezacaftor/ivacaftor was generally well tolerated and had a safety profile consistent with that seen in EVOLVE and EXPAND.

Triple Combination Regimens

"Preliminary Safety and Efficacy of Triple Combination CFTR Modulator Regimens in CF." Poster 777. Oral presentation during Workshop W18--NT: Innovative Approaches to CF Therapy.

Previously announced data from Phase 1 and Phase 2 studies of three different next-generation correctors (VX-440, VX-152 and VX-659) in combination regimens with tezacaftor and ivacaftor were presented for the first time. These data demonstrate the potential to treat the underlying cause of CF in people who have one *F508del* mutation and one minimal function mutation not responsive to ivacaftor, tezacaftor or the combination of tezacaftor/ivacaftor, a severe and difficult-to-treat type of the disease. All studies showed statistically significant improvements in lung function ($ppFEV_1$) with a triple combination regimen in these patients. In addition, initial data from the studies of VX-440 and VX-152 showed improvements in lung function with the addition of either next-generation corrector in people with two copies of the *F508del* mutation who were already receiving tezacaftor/ivacaftor. The triple combination regimens were generally well tolerated across all three studies, and the majority of adverse events were mild to moderate in severity. Across the studies, the discontinuation rate due to adverse events was low.

Data from additional ongoing Phase 2 studies are expected in early 2018. Vertex plans to initiate pivotal development of up to two triple combination regimens in the first half of 2018.

About Cystic Fibrosis

Cystic fibrosis 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 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 protein 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 ORKAMBI® (lumacaftor/ivacaftor)

In people with two copies of the *F508del* mutation, the CFTR protein is not processed and trafficked normally within the cell, resulting in little-to-no CFTR protein at the cell surface. Patients with two copies of the *F508del* mutation are easily identified by a simple genetic test.

ORKAMBI is a combination of lumacaftor, which is designed to increase the amount of mature protein at the cell surface by targeting the processing and trafficking defect of the F508del-CFTR protein, and ivacaftor, which is designed to enhance the function of the CFTR protein once it reaches the cell surface. It is an oral pill taken every 12 hours - once in the morning and once in the evening.

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 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 designed to keep CFTR proteins at the cell surface open longer to improve the transport of salt and water across the cell membrane, which helps hydrate and clear mucus from the airways. KALYDECO is available as 150 mg tablets for adults and pediatric patients age 6 years and older, and is taken with fat-containing food. It is also available as 50 mg and 75 mg granules in pediatric patients ages 2 to less than 6 years and is administered with soft-food or liquid with fat-containing food.

People with CF who have specific mutations in the *CFTR* gene are currently benefiting from KALYDECO in 27 different countries across North America, Europe and Australia.

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 at least one mutation in their CF gene that is responsive to KALYDECO. Patients should talk to their doctor to learn if they have an indicated CF gene mutation. 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 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.

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's Innovation District. Today, the company has research and development sites and commercial offices in the United States, Europe, Canada and Australia. 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 eight 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), tezacaftor, VX-440, VX-152 and VX-659 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, statements in the second and sixth paragraphs and statements regarding the timing of and development plan with respect to the next-generation triple combination regimens. 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 Vertex could experience unforeseen delays in conducting its development programs 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.

(VRTX-GEN)

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