Vertex Data Presented at European Cystic Fibrosis Society (ECFS) Conference Demonstrate Early and Long-Term Disease-Modifying Potential of Treating the Underlying Cause of CF

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- Data from KALYDECO® (ivacaftor) studies show the potential to modify the long-term progression of the disease -

- Interim analysis of the ongoing extension study of tezacaftor/ivacaftor combination (approved in the U.S. as SYMDEKO™) continues to demonstrate consistent safety and sustained benefits up to 48 weeks -

- Studies of investigational triple combination regimens highlight continued progress toward developing medicines to treat the underlying cause of the disease for up to 90 percent of people living with CF -

BELGRADE, Serbia--(BUSINESS WIRE)--Jun. 7, 2018-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced 10 scientific abstracts from the company's portfolio of cystic fibrosis (CF) medicines are being presented at the 41 stEuropean Cystic Fibrosis Conference taking place June 6-9, 2018, in Belgrade, Serbia. Collectively, the data support the potential disease-modifying benefits of treating the underlying cause of CF and Vertex's progress toward enhancing and expanding treatment options for all people living with CF.

Data from the ongoing Phase 3, open-label ARRIVALstudy presented at an oral session and published online today in *The Lancet Respiratory Medicine* show that treatment with KALYDECO® (ivacaftor) resulted in substantial decreases in mean sweat chloride as well as improvements to multiple efficacy endpoints, suggesting the potential to preserve pancreatic function and modify the course of CF beginning in children as young as one year of age. In addition, final annual analyses of the completed, five-year, post-approval observational safety study of KALYDECO show that patients taking KALYDECO had lower risk of death, transplantation, hospitalization and pulmonary exacerbations compared to patients who were matched on age, gender and genotype class who did not receive KALYDECO. Together, these studies provide further support for the benefit of both early and long-term treatment with CFTR modulators.

Results from an interim analysis of the ongoing, 96-week EXTEND Phase 3 rollover study of tezacaftor/ivacaftor combination, approved in the U.S. as SYMDEKO™ (tezacaftor/ivacaftor and ivacaftor) also add to the growing body of evidence supporting the benefit of long-term treatment of the underlying cause of the disease. Analysis presented during a poster presentation shows that the initial improvements in lung function (measured by the absolute change in percent predicted forced expiratory volume in one second [$ppFEV_1$]) observed in the Phase 3 EVOLVE study of patients homozygous for *F508del* were sustained for up to 48 weeks (24 weeks in EVOLVE + 24 weeks in EXTEND). Treatment was well-tolerated, demonstrating a safety profile consistent with that observed in the pivotal EVOLVE and EXPAND studies. Improvements across some secondary endpoints that were observed in the parent study were maintained in patients homozygous for *F508del* (n=459).

Previously announced data from Phase 1 and Phase 2 studies of three different next-generation correctors in combination regimens with tezacaftor and ivacaftor presented in an oral session highlight continued progress toward developing one medicine to treat up to 90 percent of people living with CF. 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 CF disease. With the goal of bringing the best regimen to people with CF, Vertex recently initiated Phase 3 studies evaluating two different triple combination regimens that contain a next-generation corrector (VX-445 or VX-659) in combination with tezacaftor and ivacaftor.

"The data presented at ECFS are further evidence that treating the cause of CF may significantly slow the progression of this disease beginning early in life, underscoring the importance of starting treatment for eligible patients as early as possible," said Reshma Kewalramani, M.D., Executive Vice President and Chief Medical Officer at Vertex. "Over the past year, we've made rapid progress in developing multiple new medicines that treat the underlying cause of CF, and today, we are closer to our goal of developing medicines for all patients with CF than ever before."

Presentation highlights include:

ARRIVAL Study: KALYDECO in Children Aged 12 to <24 months

"A phase 3, 2-part, single-arm study of ivacaftor treatment in patients < 2 years with a CFTR gating mutation: results from the ARRIVAL study in patients 1 to 2 years." Oral presentation WS01.1 during Workshop WS01--Exciting News from CFTR Modulator Clinical Trials.

Results from the ongoing, open-label, Phase 3 ARRIVAL study of 25 children with CF aged 12 to <24 months who have one of 10 mutations in the *CFTR* gene (*G551D*, *G178R*, *S549N*, *S549R*, *G551S*, *G1244E*, *S1251N*, *S1255P*, *G1349D* or *R117H*) show treatment with KALYDECO for 24 weeks demonstrated a safety profile consistent with that observed in previous Phase 3 studies of older children and adults. Most adverse events were mild or moderate in severity, and no patient discontinued due to adverse events. The most common adverse events (≥30%) were cough (74%), pyrexia (37%), elevated aspartate aminotransferase (37%), elevated alanine aminotransferase (32%) and runny nose (32%). Serious adverse events were observed in two patients. Two patients had elevated liver enzymes greater than eight times the upper limit of normal, but continued to receive KALYDECO after a dose interruption.

Mean baseline sweat chloride for the children in this study was 104.1 mmol/L (n=14). Following 24 weeks of treatment with KALYDECO, the mean sweat chloride level was 33.8 mmol/L (n=14). In 10 subjects with paired sweat chloride samples at baseline and Week 24, there was a mean absolute change of -73.5 mmol/L. Sweat chloride is used as a tool to diagnose infants with CF, where levels greater than or equal to 60 mmol/L indicate that CF is likely, levels of 30-59 mmol/L indicate CF is possible and levels less than 30 indicate that CF is unlikely. In the study, 10 patients had greater than 40 mmol/L decreases in sweat chloride at week 24 and four of these patients had sweat chloride levels of less than 30 mmol/L at week 24. Improvements

in multiple exploratory efficacy endpoints that measured exocrine pancreatic biomarkers, including levels of fecal elastase, serum immunoreactive trypsinogen (IRT), amylase and lipase levels, were also observed and suggest the potential for ivacaftor to protect against progressive exocrine pancreatic dysfunction when initiated at an early age.

These results supported submissions to the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) for KALYDECO in children aged 12 to <24 months.

KALYDECO Long-Term, Real-World Clinical Safety and Patient Outcomes

"Real-world outcomes in patients with cystic fibrosis treated with ivacaftor: 2016 US and UK cystic fibrosis Registry analyses." Poster IPD2.02 during Session IPD2--What do We Learn from CFTR Modulator Use in Real Life.

"Disease progression in patients with cystic fibrosis treated with ivacaftor: analyses of real-world data from the US and UK cystic fibrosis Registries." Poster IPD2.01 during Session IPD2.

Analyses of 2016 data from the fifth and final year of the completed, five-year, post-approval observational safety study of KALYDECO is the largest analyses of KALYDECO patients to date, and adds to the growing body of evidence showing that treating the underlying cause of CF has the potential to modify the course of disease in a real-world setting. In the U.S., data from 1,858 patients treated with KALYDECO show they had significantly lower risks of death, transplantation, hospitalizations and pulmonary exacerbations compared to matched untreated patients over the course of the fifth year of the study. In the U.K., data from 462 patients show similar trends. In both registries, the prevalence of the majority of evaluated CF complications and common bacterial pathogens tended to be lower in KALYDECO-treated patients.

Additional, longer-term analyses of patients who received KALYDECO for up to 5 years (635 patients in the U.S.) or up to 4 years (247 patients in the U.K.) show that patients on KALYDECO had consistently better preserved lung function, improved nutritional measures, reduced frequency of pulmonary exacerbations and hospitalizations and favorable trends in prevalence of CFRD and *Pseudomonas aeruginosa* compared to matched untreated patients. These findings were consistent with previous interim analyses. No new safety concerns were identified.

Additional Presentations

In addition to the studies noted above, other oral presentations accepted for ECFS include:

- **VOCAL:** An interim analysis from an ongoing multinational (UK, Italy, Netherlands) observational study to assess real-world effectiveness of KALYDECO in patients with a non-G551D gating mutation (*G178R*, *S549N*, *S549R*, *G551S*, *G1244E*, *S1251N*, *S1255P* or *G1349D*) was presented as an oral presentation and demonstrates sustained improvements in ppFEV$_1$, pulmonary exacerbations and BMI over 12 months compared to the 12 month pre-KALYDECO period. The reduction in ppFEV$_1$ rate of decline is further evidence that KALYDECO is a disease-modifying therapy for treating CF.
- **ORKAMBI® 2-5:** Results from a Phase 3 study of ORKAMBI in children aged 2 to 5 years homozygous for the *F508del* mutation (n=60) were presented as an oral presentation and show treatment was generally safe and well tolerated for 24 weeks. The most common adverse event (≥30%) was cough (63%); most adverse events were mild or moderate in severity. Four patients experienced serious adverse events (2 pulmonary exacerbations, 1 gastroenteritis, 1 constipation) and three patients discontinued treatment due to treatment emergent adverse events or elevated liver function tests. Improvements were observed in secondary efficacy endpoints at week 24 as demonstrated by a mean decrease in sweat chloride of 31.7 mmol/L, improvements in growth parameters (BMI, weight, stature) and biomarkers of pancreatic function. These data supported the recent submission of regulatory applications for approval in the U.S. and EU.

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 proteins 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 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) U.S. 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 U.S. Prescribing Information for KALYDECO.

About SYMDEKO™ (tezacaftor/ivacaftor and ivacaftor)

Some mutations result in CFTR protein that is not processed or folded normally within the cell, and that generally does not reach the cell surface. SYMDEKO is a combination of tezacaftor and ivacaftor. Tezacaftor is designed to address the trafficking and processing defect of the CFTR protein to enable it to reach the cell surface where ivacaftor can increase the amount of time the protein stays open.

U.S INDICATION AND IMPORTANT SAFETY INFORMATION FOR SYMDEKO™ (tezacaftor/ivacaftor and ivacaftor) tablets

SYMDEKO is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have two copies of the *F508del* mutation, or who have at least one mutation in the CF gene that is responsive to treatment with SYMDEKO. Patients should talk to their doctor to learn if they have an indicated CF gene mutation. It is not known if SYMDEKO is safe and effective in children under 12 years of age.

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

Before taking SYMDEKO, patients should tell their doctor if they: have or have had liver problems; have kidney problems; are pregnant or plan to become pregnant because it is not known if SYMDEKO will harm an unborn baby; are breastfeeding or planning to breastfeed because it is not known if SYMDEKO passes into breast milk.

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

SYMDEKO may cause dizziness in some people who take it. Patients should not drive a car, use machinery, or do anything that requires alertness until they know how SYMDEKO affects them.

Patients should avoid food or drink that contains grapefruit or Seville oranges while they are taking SYMDEKO.

SYMDEKO can cause serious side effects, including:

High liver enzymes in the blood, which have been reported in people treated with SYMDEKO or treated with ivacaftor alone. The patient's doctor will do blood tests to check their liver before they start SYMDEKO, every 3 months during the first year of taking SYMDEKO, and every year while taking SYMDEKO. 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 the skin or the white part of the eyes; loss of appetite; nausea or vomiting; dark, amber-colored urine.

Abnormality of the eye lens (cataract) in some children and adolescents treated with SYMDEKO or with ivacaftor alone. If the patient is a child or adolescent, their doctor should perform eye examinations before and during treatment with SYMDEKO to look for cataracts.

The most common side effects of SYMDEKO include headache, nausea, sinus congestion, and dizziness.

These are not all the possible side effects of SYMDEKO.

Please click here to see the full U.S. Prescribing Information for SYMDEKO.

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.

U.S. 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 U.S. Prescribing Information for ORKAMBI.

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 seven 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), SYMDEKO™ (tezacaftor/ivacaftor and ivacaftor), VX-440, VX-152, VX-659 and VX-445 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. Kewalramani's statements in the fifth paragraph of the press release. 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 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.

(VRTX-GEN)

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