Vertex Data Presented at North American Cystic Fibrosis Conference (NACFC) Demonstrate Rapid Progress Toward Expanding and Enhancing Options for Treating the Underlying Cause of Cystic Fibrosis

October 18, 2018

- Phase 2 results of VX-659 and VX-445 triple combination regimens concurrently published in The New England Journal of Medicine -

- Phase 3 ARRIVAL data support treating the underlying cause of cystic fibrosis with KALYDECO® *(ivacaftor) as early as six months of age -*

- Patient-reported outcomes data from Phase 3 EVOLVE and EXPAND studies continue to support the clinical benefit of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) -

DENVER--(BUSINESS WIRE)--Oct. 18, 2018-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced that eight scientific abstracts from the company's portfolio of cystic fibrosis (CF) medicines are being presented at the 32 ndNorth American Cystic Fibrosis Conference taking place October 18-20, 2018 in Denver.

Key highlights include presentations of Phase 2 data evaluating clinical safety and efficacy as well as *in vitro* data of two triple combination regimens (VX-659, tezacaftor and ivacaftor; VX-445, tezacaftor and ivacaftor) in patients with one *F508del* mutation and one minimal function mutation (*F508del*/Min) and in patients with two *F508del* mutations (*F508del*/*F508del*), as well as in once-daily triple combination regimens (VX-659, tezacaftor and VX-561; VX-445, tezacaftor and VX-561) in *F508del*/Min patients. Data from these studies were also published online today in *The New England Journal of Medicine (NEJM)*.

Phase 3 KALYDECO® (ivacaftor) data from ARRIVAL, the first study of KALYDECO in infants six to <12 months old with a cystic fibrosis transmembrane conductance regulator (CFTR) gating or R117H mutation is also being presented.

"The data we are presenting at this year's Conference reinforce our belief that treating the underlying cause of CF early in life may modify the course of this disease, and demonstrate the rapid progress we are making toward our goal of developing a single medicine that will treat the underlying cause of CF in up to 90 percent of people with this devastating disease," said Reshma Kewalramani, M.D., Executive Vice President and Chief Medical Officer at Vertex.

Presentation highlights include:

VX-659/Tezacaftor/Ivacaftor – Phase 2 Triple Combination Results

"Preliminary safety and efficacy of the triple combination CFTR modulator regimen VX-659/TEZ/IVA in CF." Poster 216 during Thematic Poster Session 01--CLIN-NT: Clinical Care in the Era of CFTR Modulators on Thursday, October 18 from 9:45 AM to 11:05 AM MT

This Phase 2 randomized, double-blind study assessed VX-659 in combination with tezacaftor and ivacaftor for 4 weeks in people with CF ages 18 and older with either *F508del*/Min or *F508del/F508del* mutations, and in combination with tezacaftor and VX-561 in patients with CF ages 18 and older with *F508del*/Min mutations. Primary endpoints included safety and tolerability, as well as efficacy measured by mean absolute change in percent predicted forced expiratory volume in one second ($ppFEV_1$)from baseline. Secondary endpoints included change in sweat chloride (SwCl) and Cystic Fibrosis Questionnaire-Revised Respiratory Domain score (CFQ-R RD).

The study met its primary endpoint and showed that treatment with the triple combination regimen resulted in statistically significant and clinically meaningful increases in lung function, as well as improvements in sweat chloride and CFQ-R RD. The improvements in the *F508del/F508del* patients were observed when VX-659 was added in people already receiving tezacaftor/ivacaftor. Most adverse events (AEs) were mild to moderate in severity. The most common AEs in this group were cough, infective pulmonary exacerbation of cystic fibrosis, headache, oropharyngeal pain and sputum increased.

The Phase 3 ECLIPSE clinical trial program assessing VX-659/tezacaftor/ivacaftor in people with CF with *F508del*/Min, who today don't have a medicine to treat the underlying cause of their disease, or *F508del/F508del* mutations is currently ongoing.

"Since the discovery of CFTR modulators, we have envisioned highly effective CFTR modulation therapy that could modify the

progression of the disease for all CF patients," said Steven M. Rowe, M.D., M.S.P.H., co-chair of Vertex's Triple Combination Steering Committee and Director of the Cystic Fibrosis Research Center at the University of Alabama at Birmingham. "These impressive results showing marked improvements in lung function and a substantial reduction in sweat chloride in patients with one or two *F508del* mutations demonstrate we are an important step closer towards achieving that goal."

VX-445/Tezacaftor/Ivacaftor – Phase 2 Triple Combination Results

"Preliminary safety and efficacy of the triple-combination CFTR modulator regimen VX-445/TEZ/IVA in CF." Poster 213 during Thematic Poster Session 01--CLIN-NT: Clinical Care in the Era of CFTR Modulators on Thursday, October 18 from 9:45 AM to 11:05 AM MT

This Phase 2, randomized, double-blind study assessed VX-445 in combination with tezacaftor and ivacaftor for 4 weeks in people with CF ages 18 and older with *F508del*/Min or *F508del/F508del* mutations, and in combination with tezacaftor and VX-561 in patients with CF ages 18 and older with *F508del/*Min mutations. Primary endpoints included safety and tolerability, as well as efficacy measured by mean absolute change in ppFEV$_1$ from baseline. Secondary endpoints included change in SwCl and CFQ-R RD.

The study met its primary endpoint and showed that treatment with the triple combination regimen resulted in statistically significant and clinically meaningful increases in lung function, as well as improvements in sweat chloride and CFQ-R RD. The improvements in the *F508del/F508del* patients were observed when VX-445 was added in people already receiving tezacaftor/ivacaftor. Most adverse events (AEs) were mild to moderate in severity. The most common AEs include cough, sputum increased, infective pulmonary exacerbation of cystic fibrosis, hemoptysis and pyrexia.

The Phase 3 AURORA clinical trial program assessing VX-445/tezacaftor/ivacaftor in people with CF with *F508del*/Min, who today don't have a medicine to treat the underlying cause of their disease, or *F508del/F508del* mutations is ongoing.

"The results from these two studies are truly exciting because they represent the potential for these regimens to provide significant clinical benefits for even more people with CF," said Jennifer Taylor-Cousar, M.D., co-chair of Vertex's Triple Combination Steering Committee and Associate Professor, Departments of Medicine and Pediatrics, Pulmonary Divisions, Medical Director of Clinical Research Services and Co-Director and Director of the CF Therapeutics Development Network, Adult CF Program, National Jewish Health, Colorado.

KALYDECO – Results from the Phase 3 ARRIVAL Study in Infants aged Six to <12 Months

"Ivacaftor Treatment In Patients 6 To < 12 Months Old With A CFTR Gating Mutation: Results Of A Phase 3, Two-Part Single Arm Study." Poster 810 during Poster Session on Thursday, October 18 from 11:15 AM to 1:45 PM MT

Results from the ongoing, open-label, Phase 3 ARRIVAL study of 17 infants with CF aged six to <12 months who have a CFTR gating (G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D) or R117H mutation showed treatment with KALYDECO for 24 weeks was generally safe and well tolerated and resulted in substantial improvements in sweat chloride, which was a secondary endpoint, indicating improved CFTR function. Additionally, patients treated with KALYDECO had increases in fecal elastase and reductions in immunoreactive trypsin/trypsinogen, lipase and amylase levels, which were exploratory endpoints, suggesting a pancreatic benefit early in life.

A total of 11 patients enrolled in the 24-week safety portion of the study, with a mean sweat chloride of 101.5 mmol/L at baseline. Following 24 weeks of treatment with KALYDECO, the safety profile was consistent with that observed in previous Phase 3 studies of older children and adults. Most AEs were mild to moderate in severity, and no patients discontinued treatment due to AEs. The most common AE (7/11 patients, 63.6%) was cough. SAEs (viral respiratory tract infection, viral rash and cough) occurred in three out of 11 patients and were assessed as not related or unlikely related to treatment with KALYDECO. The mean sweat chloride level was reduced by 58.6 mmol/L to 43.1 mmol/L for the six patients with both baseline and Week 24 sweat chloride measurements. Sweat chloride is used as a tool to diagnose 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.

The study is ongoing in infants younger than six months old. These data support Vertex's planned submissions to the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) for KALYDECO in children aged 6 to <12 months later this year.

Additional Presentations

In addition to the studies noted above, other presentations at NACFC include:

- **EVOLVE AND EXPAND PATIENT-REPORTED OUTCOMES (PRO):** Data were reported on PRO analyses of tezacaftor/ivacaftor treatment from the Phase 3 EVOLVE and EXPAND studies. The two randomized, double-blind, placebo-controlled trials in patients 12 years and older resulted in patient-reported improvements in outcomes beyond respiratory symptoms, including health perceptions and physical functioning, further supporting the value of tezacaftor/ivacaftor treatment in patients with CF with *F508del/F508del* mutations or with one *F508del* mutation and one residual function mutation (*F508del*/RF).(Poster 308 and 309)
- **EVOLVE, EXPAND, EXTEND RETROSPECTIVE ANALYSIS:** Researchers conducted a retrospective analysis of Phase 3

studies assessing tezacaftor/ivacaftor in patients 12 years or older with CF with *F508del/F508del* mutations (EVOLVE) and in those with an *F508del*/RF mutation (EXPAND, which also assessed ivacaftor), as well as in an ongoing open-label extension study (EXTEND). Results indicated that treatment with tezacaftor/ivacaftor improves lung function in *F508del/F508del* and *F508del*/RF patients by reducing airway resistance and improving breathing capacity. (Poster 135)

- **BRIO INTERIM RESULTS:** BRIO is an ongoing observational, non-interventional, multi-center study in patients with CF treated with KALYDECO in the conditions of a real-world setting in France. Findings from the 12-month interim analysis in patients six years and older demonstrated that the real-world effectiveness of KALYDECO in France is consistent with results from Phase 3 trials, including improvement in $ppFEV_1$, body mass index (BMI) and rate of pulmonary exacerbations (PEx). (Poster 34)
- **KALYDECO REAL-WORLD ANALYSIS:** A five-year, real-world analysis of subgroups of pediatric, adolescent and adult patients treated with KALYDECO from the U.S. Cystic Fibrosis Registry found no new safety concerns and consistent clinical benefits relative to comparators, continuing to support disease modification with the treatment. (Poster 22)

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 oral granules for weight-based dosing 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 12 months 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 12 months 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 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'sInnovation District. Today, the company has research and development sites and commercial offices in the United States, Europe, Canada, Australia and Latin America. 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), 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, the statements in the fourth, eighth and twelfth paragraphs of the press release and statements regarding (i) ongoing clinical trials, including the Phase 3 ECLIPSE trial, the Phase 3 AURORA trial and the Phase 3 ARRIVAL trial in patients less than 6 months of age and (ii) planned regulatory submissions to the FDA and EMA. 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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