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Vertex Announces Positive Results from Open-Label Phase 3 Study of KALYDECO® (ivacaftor) in Children with Cystic Fibrosis Ages 1 to 2 Years

-Study met primary safety endpoint and showed improvements across multiple endpoints, including measures of pancreatic function-

-Potential to modify the course of CF in children as young as one year of age-

-Results support FDA and EMA filings in the first quarter of 2018-

BOSTON--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced positive results from an open-label Phase 3 study of KALYDECO® (ivacaftor) in children with cystic fibrosis (CF) ages 1 to 2 years who have one of 10 mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. The ARRIVAL study met its primary endpoint of safety, showing that ivacaftor was generally well tolerated, and safety data were consistent with those seen in previous Phase 3 studies of ivacaftor in children ages 2 to 5 years and 6 to 11 years. There was also a substantial improvement in sweat chloride, a secondary endpoint, as well as in multiple exploratory endpoints evaluating pancreatic function. These data suggest the potential to modify the course of CF in children as young as one year of age. The study is ongoing in infants younger than one year old. Based on these results, Vertex plans to submit applications for ivacaftor in children ages 1 to 2 years to the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in the first quarter of 2018.

"We know that cystic fibrosis is a progressive disease with organ damage already present at birth, so the earlier patients can begin treatment, the greater their potential for improved outcomes," said Jane Davies, M.D., Royal Brompton Hospital and Imperial College, London, co-lead investigator of the ARRIVAL study. "These results are incredibly exciting: they suggest that we can begin treating the underlying cause of cystic fibrosis with KALYDECO in children as young as one year of age."

"We have a significant body of evidence demonstrating KALYDECO's immediate and long-term benefits and its potential to modify the course of CF," said Jeffrey Chodakewitz, M.D., Executive Vice President and Chief Medical Officer at Vertex. "These results are an important step in our goal of treating children as early as possible to intervene in this progressive disease."

KALYDECO is currently approved by the FDA for the treatment of CF in patients ages 2 and older who have one of 38 ivacaftor-responsive mutations in the *CFTR* gene.

About the ARRIVAL Study

ARRIVAL is an ongoing 2-part, open-label Phase 3 study assessing ivacaftor in children with CF younger than 2 years of age who have one of the following ten mutations in the *CFTR* gene: *G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D* or *R117H*. Part A of the study is evaluating the safety and pharmacokinetics of ivacaftor for five days to support the evaluation of ivacaftor for 24 weeks in Part B of the study. Part B is evaluating the safety, pharmacokinetics and efficacy of ivacaftor for 24 weeks. The primary endpoint of Part B of the study is safety, and secondary endpoints include pharmacokinetics and absolute change in sweat chloride. There are several exploratory endpoints, including ones evaluating pancreatic function. Data reported today are from Part B of the study in children ages 1 to 2 years; Parts A and B of the study in infants younger than one year old are ongoing. Of the 18 children who completed Part B of the 24-week study, 17 enrolled in a rollover study to continue receiving ivacaftor treatment. The only participant not to continue in the rollover study was older than 2 years of age, so elected to begin treatment with commercial ivacaftor.

Key results from Part B of the ARRIVAL study in children ages 1 to 2 (n=19) are below.

Safety: The study met its primary endpoint of safety. Safety data from this interim analysis were consistent with those observed in previous Phase 3 studies in children ages 2 to 5 years and 6 to 11 years. Ivacaftor was generally well tolerated through 24 weeks of treatment and the majority of adverse events were mild or moderate in severity. No patients discontinued treatment due to adverse events. The most common adverse events (≥30%) were cough, pyrexia (fever),

elevated liver enzymes and rhinorrhea (runny nose). Serious adverse events were reported in two patients; one patient had cough that was treated with IV antibiotics and one patient had a viral infection followed by distal intestinal obstruction syndrome and constipation. Two different patients experienced elevated liver enzymes of greater than eight times the upper limit of normal. Both patients had concurrent illnesses during these elevations; upon subsequently resuming ivacaftor treatment neither patient experienced any further elevations.

Sweat Chloride: Elevated sweat chloride levels are a diagnostic hallmark in CF and are the result of CFTR protein dysfunction. A reduction in sweat chloride is considered to be a marker of improved CFTR function. People with CF typically have elevated sweat chloride levels in excess of 60 mmol/L, while normal values are typically less than 30-40 mmol/L.

In Part B of the ARRIVAL study in children ages 1 to 2 years, the baseline sweat chloride level was 104.1 mmol/L (n=14). There was a mean absolute decrease of -73.5 mmol/L (n=10) in sweat chloride levels at 24 weeks of ivacaftor treatment; the median sweat chloride level at the end of the study was 31.5 mmol/L (n=14).

Pancreatic Function: In children with CF, pancreatic insufficiency is one of the most significant clinical manifestations of the disease. Pancreatic insufficiency is also the most common gastrointestinal complication of CF. There are several ways of evaluating pancreatic function in CF. Low levels, or the complete absence, of elastase in the stool (known as fecal elastase) are suggestive of pancreatic insufficiency; normal levels of fecal elastase are above 200 µg/g. High levels of a chemical made by the pancreas called immunoreactive trypsinogen (IRT) are suggestive of pancreatic obstruction. High levels of the pancreatic enzymes lipase and amylase are suggestive of pancreatitis, a known complication of CF, which can lead to progressive pancreatic damage.

In Part B of the ARRIVAL study in children ages 1 to 2 years, the baseline fecal elastase level was 182.2 µg/g (n=19). There was a mean absolute improvement in fecal elastase of 164.7 µg/g, which was an exploratory endpoint, at 24 weeks of the study; the median fecal elastase level at the end of the study was 357.0 µg/g (n=15). There were also decreases in the exploratory endpoint of IRT and in the safety assessments of lipase and amylase, which suggest improvement in pancreatic sufficiency and early pancreatic benefit.

Full results from the study will be submitted for presentation at an upcoming medical conference.

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 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, the statements in the second and third paragraphs and statements regarding the expected timing of regulatory applications to be submitted to the FDA and EMA. 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, (i) that

the initial results set forth in this press release may differ from the final results from this ongoing study, (ii) that regulatory authorities may not approve, or approve on a timely basis, ivacaftor in these patient populations due to safety, efficacy or other reasons, and (iii) 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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