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Phase 3 Studies of the Tezacaftor/Ivacaftor Combination Treatment in People with Cystic Fibrosis Ages 12 and Older Published in the New England Journal of Medicine

- Data showed significant improvements in lung function (ppFEV$_1$) with a favorable safety profile across multiple patient groups -

- Tezacaftor/ivacaftor currently under review by the FDA and EMA; FDA Priority Review action date of February 28, 2018 -

BOSTON--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) announced today that the *New England Journal of Medicine (NEJM)* published two articles with results from two Phase 3 studies of the tezacaftor/ivacaftor combination treatment, a medicine in development that is designed to treat the underlying cause of cystic fibrosis (CF) in people ages 12 and older who have certain mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. In both studies, the tezacaftor/ivacaftor combination demonstrated statistically significant and clinically meaningful improvements in lung function and other measures of disease. The EVOLVE study evaluated the combination in people who have two copies of the *F508del* mutation, the most common mutation in the *CFTR* gene. The EXPAND study evaluated the combination in people with one *F508del* mutation and one mutation that results in residual CFTR function. The results were published in two online articles today in conjunction with two oral presentations at the 31st Annual North American Cystic Fibrosis Conference, November 2 to 4, 2017 in Indianapolis. These data formed the basis of applications for the approval of the tezacaftor/ivacaftor combination that are currently under review with regulatory agencies in the United States and Europe. In the United States, the Food and Drug Administration (FDA) has granted Priority Review of the application and has set an action date of February 28, 2018.

"We have made unprecedented progress in the treatment of CF in recent years, but we continue to drive ourselves to deliver even greater benefits for patients today and more new medicines for patients who are still waiting," said Jeffrey Chodakewitz, M.D., Executive Vice President and Chief Medical Officer at Vertex. "These tezacaftor/ivacaftor results are exciting because they represent the potential to do both."

Summary of Key Data from EVOLVE

The 24-week EVOLVE study evaluated tezacaftor/ivacaftor in more than 500 people with CF ages 12 and older who have two copies of the *F508del* mutation. Improvements across multiple disease measures, including lung function, were demonstrated among patients treated with tezacaftor/ivacaftor compared to those who received placebo. There was also a reduction in pulmonary exacerbations among those treated with tezacaftor/ivacaftor.

"In this study, the tezacaftor/ivacaftor combination demonstrated significant, clinically meaningful improvements in lung function and other measures of cystic fibrosis health status," said Jennifer Taylor-Cousar, M.D., co-lead author of the EVOLVE study 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. "Tezacaftor/ivacaftor was also very well tolerated, which makes it an important potential new option for helping our patients feel better and change the course of their disease. The fact that tezacaftor/ivacaftor will be the basis of triple combination therapy makes this positive data even more exciting for patients with CF and the physicians who care for them."

Lung Function: Progressive lung disease is a major source of illness and is the leading cause of death in people with CF. The study met its primary endpoint with a mean absolute improvement in lung function (measured as percent predicted forced expiratory volume in one second, or ppFEV$_1$) through 24 weeks of 4.0 percentage points from baseline compared to placebo ($p < 0.0001$). This equates to a mean relative improvement (a key second endpoint in the study), which is an assessment of the percentage change, of 6.8 percent ($p < 0.0001$).

Pulmonary Exacerbations: Pulmonary exacerbations are episodes of worsening signs and symptoms of the disease that often require treatment with intravenous antibiotics or hospitalization. Through the 24-week study, those receiving tezacaftor/ivacaftor had a 35 percent reduction in the annualized rate of pulmonary exacerbations compared to those on placebo (p=0.0054). In addition, patients receiving tezacaftor/ivacaftor were 47 percent less likely to experience a pulmonary exacerbation that required hospitalization or intravenous antibiotics than those receiving placebo (p=0.0042).

Body Mass Index: Body mass index, or BMI, is a measure of body fat based on a person's height and weight. For people with CF, BMI is one way of assessing nutritional status; poor nutritional status, and thus lower BMI, is associated with worse lung function. In EVOLVE, people receiving tezacaftor/ivacaftor had a non-statistically significant BMI increase of 0.06 compared to those receiving placebo (p=0.4127).

Patient-Reported Outcomes: The Cystic Fibrosis Questionnaire — Revised (CFQ-R) is a validated patient-reported outcome tool that was used in the EVOLVE study to measure the impact of tezacaftor/ivacaftor on overall health, daily life, perceived well-being and symptoms. One aspect of the CFQ-R, referred to as the respiratory domain, addresses patient reported symptoms including things such as coughing, congestion, wheezing and other respiratory symptoms. In EVOLVE, the mean absolute improvement in the respiratory domain of CFQ-R at Week 24 was 5.1 compared to those receiving placebo ($p < 0.0001$). This increase is considered nominally statistically significant.

Safety: The tezacaftor/ivacaftor combination treatment was generally well tolerated. The majority of adverse events were mild or moderate. The most common adverse events (≥15%), regardless of treatment group, were infective pulmonary exacerbation, cough, headache, nasopharyngitis and sputum increased. The rate of discontinuations due to adverse events was low and similar between the placebo group and the combination treatment group. Rates of adverse events, serious adverse events and respiratory-related adverse events were similar between the placebo and the tezacaftor/ivacaftor combination treatment groups.

Summary of Key Data from EXPAND

The EXPAND study evaluated eight weeks of treatment with the tezacaftor/ivacaftor combination, ivacaftor monotherapy or placebo in approximately 250 people with CF ages 12 and older who have one *F508del* mutation and one mutation that results in residual CFTR function. Improvements across multiple disease measures, including lung function, were demonstrated among patients treated with tezacaftor/ivacaftor and those treated with ivacaftor alone in the study compared to those who received placebo.

"This is an exciting time to be part of cystic fibrosis research as we continue to improve outcomes for patients," said Steven M. Rowe, M.D., M.S.P.H., co-lead author of the EXPAND study and Professor of Medicine, Pediatrics, and Cell, Developmental and Integrative Biology, Director of the Gregory Fleming James Cystic Fibrosis Research Center, Nancy and Eugene Gwaltney Endowed Chair in Medical Research, University of Alabama at Birmingham. "These results are particularly exciting because they demonstrate that by addressing the underlying cause of cystic fibrosis, the tezacaftor/ivacaftor combination offers significant benefits for many people with this severe and life-shortening disease, while also offering increased benefit over KALYDECO alone in patients with residual function mutations."

Lung Function: The EXPAND study met its primary endpoint of absolute improvement in lung function, with those receiving tezacaftor/ivacaftor demonstrating a mean absolute improvement of 6.8 percentage points compared to placebo ($p < 0.0001$) and the ivacaftor monotherapy group demonstrating a mean absolute improvement of 4.7 percentage points compared to placebo ($p < 0.0001$). Improvements in lung function were measured as the change in $ppFEV_1$ from the start of the study (baseline) to the average of the Week 4 and Week 8 measurements. An additional pre-specified analysis showed that the tezacaftor/ivacaftor combination treatment provided a statistically significant improvement in $ppFEV_1$ over ivacaftor alone (2.1 percentage points, $p < 0.0001$).

Patient-Reported Outcomes: In EXPAND, the mean absolute improvement in the respiratory domain of CFQ-R (the key secondary endpoint), measured as the average of the Week 4 and Week 8 measurements, was 11.1 for those receiving tezacaftor/ivacaftor and was 9.7 for those receiving ivacaftor, both compared to placebo ($p < 0.0001$).

Safety: In the EXPAND study, the safety profile observed for the tezacaftor/ivacaftor combination treatment was favorable and similar to that seen in the EVOLVE study. Tezacaftor/ivacaftor combination treatment and ivacaftor monotherapy were both generally well tolerated. The majority of adverse events were mild or moderate. The most common adverse events (≥15%), regardless of treatment group, were cough and infective pulmonary exacerbation. There were no discontinuations due to adverse events in the combination treatment group. Discontinuations due to adverse events were low and similar between the placebo group and the ivacaftor monotherapy group. The incidence of adverse events, serious adverse events and respiratory-related adverse events was similar between the placebo, tezacaftor/ivacaftor combination and ivacaftor monotherapy groups.

About Cystic Fibrosis

Cystic Fibrosis (CF) 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 cystic fibrosis transmembrane conductance regulator (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.

In people with the *F508del* mutation, the CFTR protein is not processed, or folded, normally within the cell and generally does not reach the cell surface. Tezacaftor is designed to address the processing defect of *F508del*-CFTR to enable it to reach the cell surface where ivacaftor can further enhance the protein's function.

In North America, Europe and Australia, there are more than 22,000 people ages 12 and older who have two copies of the *F508del* mutation, and there are more than 1,500 people ages 12 and older who have at least one residual function mutation that is responsive to tezacaftor/ivacaftor in vitro or in the clinic.

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, fourth and eleventh paragraphs and statements regarding the tezacaftor/ivacaftor combination and the timing of the potential regulatory approval of the tezacaftor/ivacaftor combination. 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, (i) that regulatory authorities may not approve, or approve on a timely basis, the tezacaftor/ivacaftor combination due to safety, efficacy or other reasons, and (ii) 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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