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Vertex Submits Applications in the U.S. and Europe for Approval of Lumacaftor in Combination with Ivacaftor for People with Cystic Fibrosis Who Have Two Copies of the F508del Mutation

-U.S. submission includes request for Priority Review; Accelerated Assessment has been granted in the EU-

-Approximately 8,500 people in the U.S. and 12,000 in Europe ages 12 and older have two copies of the F508del mutation-

BOSTON--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced the submission of a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) and a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) for a fully co-formulated combination of lumacaftor (400mg q12h) and ivacaftor (250mg q12h) for people with cystic fibrosis (CF) ages 12 and older who have two copies of the F508del mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. There are approximately 22,000 people with CF ages 12 and older who have two copies of the F508del mutation in North America, Europe and Australia, including approximately 8,500 in the United States and 12,000 in Europe.

"The combination of lumacaftor and ivacaftor is the first potential treatment designed to target the underlying cause of cystic fibrosis in people with two copies of the F508del mutation, which is the most common form of the disease," said Jeffrey Chodakewitz, M.D., Executive Vice President and Chief Medical Officer at Vertex. "Today's submissions represent important progress toward our ongoing efforts to develop new medicines for the vast majority of people with cystic fibrosis, and we look forward to working closely with regulatory agencies to bring this treatment to eligible patients as quickly as possible."

In the U.S., the combination of lumacaftor and ivacaftor received Breakthrough Therapy Designation in late 2012. The U.S. submission includes a request for Priority Review, which, if granted, would shorten the FDA's anticipated review time from approximately 12 to 8 months. The European Committee for Medicinal Products for Human Use (CHMP) has granted Vertex's request for Accelerated Assessment of the MAA, which is given to new medicines of major public health interest and shortens the review time from approximately 210 to 150 days for the CHMP to give an opinion following the start of the review. The CHMP opinion is then reviewed by the European Commission, which generally issues a final decision within three months. If approved, Vertex would then begin the country-by-country reimbursement approval process. Both applications seek approval for a fully co-formulated combination treatment dosed as two tablets every 12 hours (four tablets daily).

The NDA and MAA submissions are based on previously announced data from two global Phase 3 studies, TRAFFIC and TRANSPORT, and the first interim data from the subsequent rollover study in people ages 12 and older who have two copies of the F508del mutation treated with standard-of-care medicines. The TRAFFIC and TRANSPORT studies showed improvements in lung function and other measures of disease, such as pulmonary exacerbations, through 24 weeks of treatment with lumacaftor in combination with ivacaftor. Initial interim data from the rollover study showed that lung function improvements were sustained for 48 total weeks of treatment (24 weeks in TRAFFIC/TRANSPORT + 24 weeks in rollover study). The combination was generally well tolerated in all three studies. In TRAFFIC and TRANSPORT, the most common adverse events were infective pulmonary exacerbation, cough, headache and increased sputum.

Cystic fibrosis is a rare genetic disease for which there is no cure. It is caused by a defective or missing CFTR protein resulting from mutations in the *CFTR* gene. The defective or missing protein results in poor flow of salt and water into and out of the cell in a number of organs, including the lungs. 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. Lumacaftor, a CFTR corrector, is designed to address the processing and trafficking defect of the F508del-CFTR protein, increasing the amount of functional protein at the cell surface where ivacaftor, a CFTR potentiator, can further enhance its function.

Expanded Access Programs

In recognition of the immediate needs of some people with CF, Vertex is working to make the combination of lumacaftor and ivacaftor available to people ages 12 and older who have two copies of the F508del mutation, are in critical medical need and meet additional eligibility criteria. In the U.S., Vertex plans to begin a Phase 3b study for a limited number of people who have severe lung disease in the first quarter of 2015, followed by an expanded access program in the second quarter of the year, pending discussions with the FDA. Vertex will also work with regulatory authorities outside the United States toward

implementing additional expanded access programs in other countries, with a goal of opening programs for eligible patients in the second quarter of 2015.

For more information, please contact Vertex Medical Information (U.S.: 1-877-634-8789 or medicalinfo@vrtx.com; outside the U.S.: vertexmedicalinfo@vrtx.com).

About the Combination

The combination of lumacaftor and ivacaftor is the first potential medicine designed to treat the underlying cause of CF in people with two copies of the F508del mutation, the most common form of the disease. In North America, Europe and Australia, there are approximately 22,000 people ages 12 and older who have two copies of the F508del mutation.

Known as a CFTR corrector, lumacaftor aims to address the processing and trafficking defect of the F508del-CFTR protein to enable it to reach the cell surface where the CFTR potentiator, ivacaftor, can further enhance the ion channel function of the CFTR protein. Ivacaftor is designed to help the CFTR channel at the cell surface open more often to improve the transport of salt and water across the cells. In combination, lumacaftor and ivacaftor are believed to help hydrate and clear mucus from the airways.

About Cystic Fibrosis

Cystic fibrosis is a rare, life-threatening genetic disease affecting approximately 75,000 people in North America, Europe and Australia. Today, the median predicted age of survival for a person with CF is between 34 and 47 years, but the median age of death remains in the mid-20s.

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 more than 1,900 known mutations in the *CFTR* gene. Some of these mutations, which can be determined by a genetic, or genotyping test, lead to CF by creating non-working or too few CFTR protein at the cell surface. The defective or missing CFTR protein results in poor flow of salt and water into and out of the cell in a number of organs, including the lungs. This leads to the buildup of abnormally thick, sticky mucus that can cause chronic lung infections and progressive lung damage.

Collaborative History with Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT)

Vertex initiated its CF research program in 1998 as part of a collaboration with CFFT, the nonprofit drug discovery and development affiliate of the Cystic Fibrosis Foundation. This collaboration was expanded to support the accelerated discovery and development of Vertex's CFTR modulators.

About Vertex

Vertex is a global biotechnology company that aims to discover, develop and commercialize innovative medicines so people with serious diseases can lead better lives. In addition to our clinical development programs focused on cystic fibrosis, Vertex has more than a dozen ongoing research programs aimed at other serious and life-threatening diseases.

Founded in 1989 in Cambridge, Mass., Vertex today has research and development sites and commercial offices in the United States, Europe, Canada and Australia. For five years in a row, *Science* magazine has named Vertex one of its Top Employers in the life sciences. For additional information and the latest updates from the company, please visit www.vrtx.com.

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. Chodakewitz's statements in the second paragraph of the press release, and the information provided regarding (i) Vertex's NDA submission to the FDA and MAA submission to the EMA, (ii) Vertex's request for priority review and (iii) Vertex's planned compassionate use program and Phase 3b study. 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 regulatory authorities may not approve, or approve on a timely basis, lumacaftor in combination with ivacaftor 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.

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