Vertex Announces European Medicines Agency Validation for Marketing Authorization Application Extension for KAFTRIO® in Combination With Ivacaftor to Include People With Cystic Fibrosis and Responsive Rare Mutations

November 24, 2023

-Application to add ~200 non-F508del CFTR mutations to the KAFTRIO® license-

-If approved, ~2,800 people with cystic fibrosis in the European Union ages 2 and above could receive a medicine that treats the underlying cause of their disease for the first time-

LONDON--(BUSINESS WIRE)--Nov. 24, 2023-- Vertex Pharmaceuticals (Nasdaq: VRTX) today announced that the European Medicines Agency (EMA) has validated a Type II variation application to the Marketing Authorization for KAFTRIO® (ivacaftor/tezacaftor/elexacaftor) in combination with ivacaftor. The application is for expansion of the approved indication for KAFTRIO® in a combination regimen with ivacaftor for the treatment of people with cystic fibrosis (CF) ages 2 and above who have a mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive based on clinical and/or *in vitro* data, including the *N1303K* mutation. The application will now be reviewed by the Committee for Medicinal Products for Human Use (CHMP), which will issue an opinion to the European Commission regarding the potential approval of this license expansion.

Data to support this submission includes the results of a Phase 3, randomized, placebo-controlled clinical study in people with rare non-*F508del* KAFTRIO®-responsive *CFTR* mutations. This study met its primary endpoint and showed that KAFTRIO® in combination with ivacaftor resulted in rapid, statistically significant, and clinically meaningful improvements in lung function compared to placebo (9.2 percentage point increase in ppFEV$_1$; P<0.0001; 95% CI [7.2, 11.3]). The medicine was generally well tolerated, with safety data generally consistent with the established safety profile of KAFTRIO® in combination with ivacaftor.

The Marketing Authorization Application submission package also includes real-world evidence data from the U.S. Cystic Fibrosis Foundation Patient Registry with respect to people with CF with non-*F508del* KAFTRIO®-responsive *CFTR* mutations who are receiving commercially available TRIKAFTA® (which is the name for KAFTRIO® in the U.S.). In addition, the submission includes *in vitro* data using a well-established laboratory model that has been the basis of approval of the rare mutations indication in the U.S.

“It is encouraging to see such positive clinical trial results for KAFTRIO in people with CF with these rare types of mutations, which are non-*F508del*,” said Professor Isabelle Fajac, Professor of Physiology, Cochin Hospital, Assistance Publique-Hôpitaux de Paris, Université Paris Cité, Paris, France. “The majority of these people currently have no treatment option to address the underlying cause of their CF, so this submission is an extremely important step towards a medicine becoming available for these people with high unmet medical needs.”

“We are committed to going the distance in cystic fibrosis and dedicated to bringing treatments to all people with CF,” said Nia Tatsis, Ph.D., Executive Vice President, Chief Regulatory and Quality Officer at Vertex. “We look forward to working with the EMA on this important submission for people with CF who have non-*F508del* KAFTRIO-responsive rare mutations, who currently cannot access KAFTRIO for the underlying cause of their disease.”

Vertex plans to submit regulatory filings for the same mutations in Australia, Brazil, Canada, New Zealand and Switzerland. The company also plans to submit a subset of these mutations, including *N1303K* and non-canonical splice mutations, not currently included in the U.S. TRIKAFTA® label to the U.S. FDA.

About Cystic Fibrosis

Cystic fibrosis (CF) is a rare, life-shortening genetic disease affecting more than 88,000 people globally. CF is a progressive, multi-organ disease that affects the lungs, liver, pancreas, GI tract, sinuses, sweat glands and reproductive tract. CF is caused by a defective and/or missing CFTR protein resulting from certain mutations in the *CFTR* gene. Children must inherit two defective *CFTR* genes — one from each parent — to have CF, and these mutations can be identified by a genetic test. While there are many different types of *CFTR* mutations that can cause the disease, the vast majority of people with CF have at least one *F508del* mutation. *CFTR* mutations lead to CF by causing CFTR protein to be defective or by leading to a shortage or absence of

CFTR protein at the cell surface. The defective function and/or absence of CFTR protein results in poor flow of salt and water into and out of the cells in a number of organs. In the lungs, this leads to the buildup of abnormally thick, sticky mucus, chronic lung infections and progressive lung damage that eventually leads to death for many patients. The median age of death is in the 30s, but with treatment, projected survival is improving.

About KAFTRIO® (ivacaftor/tezacaftor/elexacaftor) in Combination With Ivacaftor

In people with certain types of mutations in the *CFTR* gene, the CFTR protein is not processed or folded normally within the cell, and this can prevent the CFTR protein from reaching the cell surface and functioning properly. KAFTRIO® (ivacaftor/tezacaftor /elexacaftor) in combination with ivacaftor is an oral medicine designed to increase the quantity and function of the CFTR protein at the cell surface. Elexacaftor and tezacaftor work together to increase the amount of mature protein at the cell surface by binding to different sites on the CFTR protein. Ivacaftor, which is known as a CFTR potentiator, is designed to facilitate the ability of CFTR proteins to transport salt and water across the cell membrane. The combined actions of ivacaftor, tezacaftor and elexacaftor help hydrate and clear mucus from the airways.

KAFTRIO® (ivacaftor/tezacaftor/elexacaftor) in combination with ivacaftor is approved in the European Union for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one copy of the *F508del* mutation in the *CFTR* gene.

For complete product information, please see the Summary of Product Characteristics that can be found on www.ema.europa.eu.

About Vertex

Vertex is a global biotechnology company that invests in scientific innovation to create transformative medicines for people with serious diseases. The company has approved medicines that treat the underlying causes of multiple chronic, life-shortening genetic diseases — cystic fibrosis, sickle cell disease and transfusion-dependent beta thalassemia — and continues to advance clinical and research programs in these diseases. Vertex also has a robust clinical pipeline of investigational therapies across a range of modalities in other serious diseases where it has deep insight into causal human biology, including APOL1-mediated kidney disease, acute and neuropathic pain, type 1 diabetes and alpha-1 antitrypsin deficiency.

Vertex was founded in 1989 and has its global headquarters in Boston, with international headquarters in London. Additionally, the company has research and development sites and commercial offices in North America, Europe, Australia and Latin America. Vertex is consistently recognized as one of the industry's top places to work, including 14 consecutive years on Science magazine's Top Employers list and one of Fortune’s 100 Best Companies to Work For. For company updates and to learn more about Vertex's history of innovation, visit www.vrtx.com or follow us on LinkedIn, YouTube and Twitter/X.

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 made by Nia Tatsis, Ph.D., and Professor Isabelle Fajac in this press release and statements regarding our expectation that, if approved for these mutations, 2,800 people with CF in the EU ages 2 and above could receive a medicine that treats the underlying cause of their disease for the first time, our expectations for a CHMP opinion regarding potential approval of this license expansion for KAFTRIO, statements regarding the potential benefits of KAFTRIO, our plans to submit regulatory filings for the same mutations in Australia, Brazil, Canada, New Zealand and Switzerland, and our plans to submit regulatory filings for a subset of these mutations to the U.S. FDA for the TRIKAFTA label. 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 data from the company’s development programs may not support a label expansion for KAFTRIO/TRIKAFTA, that regulatory authorities may not approve a label expansion for KAFTRIO/TRIKAFTA on a timely basis or at all, and other risks listed under the heading “Risk Factors” in Vertex's annual report and in subsequent filings filed with the Securities and Exchange Commission and available through the company's website at www.vrtx.com and www.sec.gov. You should not place undue reliance on these statements, or the scientific data presented. Vertex disclaims any obligation to update the information contained in this press release as new information becomes available.

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