Vertex to Initiate Phase 3 Development Program for New Once-Daily Triple Combination Regimen in People With Cystic Fibrosis

July 28, 2021

- Phase 2 study met primary endpoint and all secondary endpoints -

- Phase 2 data demonstrated that a once-daily triple combination of VX-121/ tezacaftor/VX-561 has potential for enhanced clinical benefit compared to TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor) -

- Initiation of Phase 3 program expected in the second half of 2021 -

BOSTON--(BUSINESS WIRE)--Jul. 28, 2021-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced the company will initiate a Phase 3 development program for the new once-daily investigational triple combination of VX-121/tezacaftor/VX-561 (deutivacaftor) in the second half of 2021. The combination of VX-121/tezacaftor/VX-561 was first identified as having potential for increased efficacy based on its ability to drive higher levels of chloride transport compared to TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor) in human bronchial epithelial cells *in vitro*. The combination of VX-121/tezacaftor/VX-561 was evaluated in a Phase 2 study in people with cystic fibrosis (CF) ages 18 and older with one *F508del* mutation and one minimal function mutation (F/MF) and in people with CF ages 18 and older with two *F508del* mutations (F/F). The regimen was generally well-tolerated, and the study met the primary efficacy endpoint of absolute change from baseline in ppFEV$_1$ and all secondary efficacy endpoints including absolute change from baseline in sweat chloride concentration in both patient populations. Taken together, these data suggest the triple combination holds the potential to restore cystic fibrosis transmembrane conductance regulator (CFTR) function in people with CF to even higher levels than seen with other Vertex CFTR modulators and thereby provide enhanced clinical benefit.

“TRIKAFTA has demonstrated high levels of efficacy in people with CF who have at least one *F508del* mutation. However, we remain committed to continuing our efforts to maximize the benefit and convenience we can deliver for these patients,” said Carmen Bozic, M.D., Executive Vice President, Global Medicines Development and Medical Affairs, and Chief Medical Officer at Vertex. “With this once-daily, next-in-class, triple combination regimen, our goal is to develop a more effective treatment regimen with the potential to restore CFTR function in people with CF to even higher levels than currently achievable.”

Phase 2 Study Results:

Results from Phase 2 study of VX-121/ tezacaftor/VX-561 in adults with one *F508del* and one minimal function mutation (F/MF). Results shown are mean absolute within-group change from baseline through Day 29*

	ppFEV$_1$ (Percentage Points)	**Sweat Chloride (mmol/L)**
F/MF Treatment Group		
Placebo n=10	+1.9 (p=0.5214)	+2.3 (p=0.6198)
VX-121 (5 mg qd)/tezacaftor (100 mg qd)/VX-561 (150 mg qd) Triple Combination Regimen n=9	+4.6 (p=0.1253)	-42.8 (p<0.0001)
VX-121 (10 mg qd)/ tezacaftor (100 mg qd)/VX-561 (150 mg qd) Triple Combination Regimen n=19	+14.2 (p<0.0001)	-45.8 (p<0.0001)
VX-121 (20 mg qd)/ tezacaftor (100 mg qd)/ VX-561 (150 mg qd) Triple Combination Regimen n=20	+9.8 (p<0.0001)	-49.5 (p<0.0001)

Results from Phase 2 study of VX-121/ tezacaftor/VX-561 in adults with two *F508del* mutations (F/F). Results shown are mean absolute within-group change from baseline (after 4-week run-in on tezacaftor/ivacaftor) through Day 29*

	ppFEV$_1$ (Percentage Points)	Sweat Chloride (mmol/L)
F/F Treatment Group		
Tezacaftor (100 mg qd)/ivacaftor (150 mg q12h) (active control) n=10	-0.1 (p=0.9635)	-2.6 (p=0.3633)
VX-121 (20 mg qd)/ tezacaftor (100 mg qd)/VX-561 (150 mg qd) Triple Combination Regimen n=18	+15.9 (p<0.0001)	-45.5 (p<0.0001)

*The primary efficacy analysis is the mean absolute within-group change from baseline in ppFEV1 through Day 29 for any VX-121/tezacaftor/VX-561 dose group.

VX-561 was also evaluated in a dose-ranging monotherapy study. Complete data from the Phase 2 clinical study of VX-121/tezacaftor/VX-561 and the VX-561 Phase 2 monotherapy study will be presented at a later date.

About the Phase 3 Program

The Phase 3 program consists of two randomized, double-blind, active-controlled 48-week trials, which will evaluate the safety and efficacy of VX-121 (20 mg)/tezacaftor (100 mg)/VX-561 (250 mg) in comparison to TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor). The first study will enroll approximately 350 people with CF ages 12 years and older with one *F508del* mutation and one minimal function mutation (F/MF). The second study will enroll approximately 450 people with CF ages 12 years and older with two *F508del* mutations (F/F) or one *F508del* mutation and a second mutation responsive to CFTR modulators. The primary endpoint in both studies is the absolute change from baseline in ppFEV$_1$, which will be analyzed for non-inferiority to TRIKAFTA. Both studies will also assess absolute change from baseline in ppFEV$_1$ and sweat chloride for superiority to TRIKAFTA®.

About VX-121/Tezacaftor/VX-561

In people with certain types of mutations in the *CFTR* gene, the CFTR protein is not processed and cannot move through the cell normally. This results in little to no protein at the cell surface. VX-121 and tezacaftor are designed to increase the amount of mature protein at the cell surface by targeting the processing and trafficking defect of the CFTR protein. VX-561 (deutivacaftor) is an investigational potentiator designed to keep CFTR proteins at the cell surface open longer to improve the flow of salt and water across the cell membrane, which helps hydrate and clear mucus from the airways. The VX-121/tezacaftor/VX-561 program was granted Fast Track and Orphan Drug Designations from the U.S. Food and Drug Administration for the treatment of cystic fibrosis.

INDICATION AND IMPORTANT SAFETY INFORMATION FOR TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor) TABLETS

What is TRIKAFTA?

TRIKAFTA is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one copy of the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene or another mutation that is responsive to treatment with TRIKAFTA. Patients should talk to their doctor to learn if they have an indicated CF gene mutation. It is not known if TRIKAFTA is safe and effective in children under 6 years of age.

Patients should not take TRIKAFTA if they take certain medicines or herbal supplements, such as: antibiotics such as rifampin or rifabutin; seizure medicines such as phenobarbital, carbamazepine, or phenytoin; or St. John’s wort.

Before taking TRIKAFTA, patients should tell their doctor about all of their medical conditions, including if they: have kidney problems; have or have had liver problems; are pregnant or plan to become pregnant because it is not known if TRIKAFTA will harm an unborn baby; or are breastfeeding or planning to breastfeed because it is not known if TRIKAFTA passes into breast milk.

TRIKAFTA may affect the way other medicines work, and other medicines may affect how TRIKAFTA works. Therefore, the dose of TRIKAFTA may need to be adjusted when taken with certain medicines. Patients should especially tell their doctor if they take: antifungal medicines including ketoconazole, itraconazole, posaconazole, voriconazole, or fluconazole; antibiotics including telithromycin, clarithromycin, or erythromycin.

TRIKAFTA may cause dizziness in some people who take it. Patients should not drive a car, operate machinery, or do anything that requires alertness until they know how TRIKAFTA affects them.

Patients should avoid food or drink that contains grapefruit while they are taking TRIKAFTA.

TRIKAFTA can cause serious side effects, including:

High liver enzymes in the blood, which is a common side effect in people treated with TRIKAFTA. These can be serious and may be a sign of liver injury. The patient's doctor will do blood tests to check their liver before they start TRIKAFTA, every 3 months during the first year of taking TRIKAFTA, and every year while taking TRIKAFTA. 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) has happened in some children and adolescents treated with TRIKAFTA. If the patient is a child or adolescent, their doctor should perform eye examinations before and during treatment with TRIKAFTA to look for cataracts.

The most common side effects of TRIKAFTA include headache, upper respiratory tract infection (common cold) including stuffy and runny nose, stomach (abdominal) pain, diarrhea, rash, increase in liver enzymes, increase in a certain blood enzyme called creatine phosphokinase, flu (influenza), inflamed sinuses, and increase in blood bilirubin.

These are not all the possible side effects of TRIKAFTA. **Please click the product link to see the full Prescribing Information for TRIKAFTA.**

About Cystic Fibrosis

Cystic Fibrosis (CF) is a rare, life-shortening genetic disease affecting more than 80,000 people globally. CF is a progressive, multi-system disease that affects the lungs, liver, GI tract, sinuses, sweat glands, pancreas 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. While there are many different types of *CFTR* mutations that can cause the disease, the vast majority of all people with CF have at least one *F508del* mutation. These mutations, which can be determined by a genetic test, or genotyping test, lead to CF by creating non-working and/or too few CFTR proteins 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 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 early 30s.

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 multiple approved medicines that treat the underlying cause of cystic fibrosis (CF) — a rare, life-threatening genetic disease — and has several ongoing clinical and research programs in CF. Beyond CF, Vertex has a robust pipeline of investigational small molecule medicines in other serious diseases where it has deep insight into causal human biology, including pain, alpha-1 antitrypsin deficiency and APOL1-mediated kidney diseases. In addition, Vertex has a rapidly expanding pipeline of cell and genetic therapies for diseases such as sickle cell disease, beta thalassemia, Duchenne muscular dystrophy and type 1 diabetes mellitus.

Founded in 1989 in Cambridge, Mass., Vertex's global headquarters is now located in Boston's Innovation District and its international headquarters is 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 11 consecutive years on Science magazine's Top Employers list and a best place to work for LGBTQ equality by the Human Rights Campaign. For company updates and to learn more about Vertex's history of innovation, visit www.vrtx.com or follow us on Facebook, Twitter, LinkedIn, YouTube and Instagram.

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 Dr. Carmen Bozic in this press release and statements regarding our expectations and plans for the Phase 3 development program for the new once-daily triple combination of VX-121/tezacaftor/VX-561, including the timing of program initiation and patient enrollment, our expectations for the benefits and potential of the new triple combination, including our beliefs for the enhanced clinical benefit compared to TRIKAFTA®, and our expectations that data from the Phase 2 studies will be presented at a later date. 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 risks and uncertainties that could cause actual events or results to differ materially from those expressed or implied by such forward-looking statements. Those risks and uncertainties include, among other things, that data from a limited number of patients may not be indicative of final clinical trial results, that the Phase 3 development program evaluating the new triple combination may not be initiated or completed on the anticipated timeline, or at all, 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 the heading “Risk Factors” in Vertex's most recent annual report and subsequent filings filed with the Securities and Exchange Commission at www.sec.gov and available through the company's website at www.vrtx.com. 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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