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Proof-of-Concept Study of Ivacaftor Monotherapy Showed Improvements in Lung Function After Two Weeks of Treatment in People with Cystic Fibrosis who have a Residual Function Mutation

-Data are consistent with in vitro observations in residual function mutations showing that ivacaftor improved CFTR activity-

-8-week open-label period showed improvements in lung function-

-Data support plans to initiate a Phase 3 study of ivacaftor in people with CF who have a residual function mutation-

BOSTON--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced the results of a two-part proof-of-concept study of ivacaftor in 24 people with cystic fibrosis (CF) who have a residual function mutation. The first part of the study evaluated ivacaftor, compared with placebo, in a two-week crossover design over two treatment cycles, and the second part of the study evaluated ivacaftor in an eight-week open-label design. In part one, a statistically significant improvement in mean absolute lung function (percent predicted forced expiratory volume in one second; $PPFEV_1$) was observed after treatment with ivacaftor for two weeks compared with placebo. In part two of the study, improvements in lung function ($PPFEV_1$) were observed after eight weeks of treatment. In the study, ivacaftor was generally well-tolerated, and the most common adverse events in the treatment group were cough and respiratory tract infection.

This proof-of-concept study was the first to evaluate the use of ivacaftor in multiple residual function mutations and is supported by *in vitro* observations that showed ivacaftor enhanced the function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein in cells with residual function mutations. Based on these data, Vertex plans to initiate a larger Phase 3 study in people with residual function mutations that will evaluate longer-duration treatment with ivacaftor, pending discussions with regulatory authorities.

There are more than 3,000 people ages 6 and older in North America, Europe and Australia who have a non-R117H residual function mutation.

"This study showed potential for ivacaftor to provide clinical benefit for many of the people who have a residual function mutation and provides important support for the initiation of a Phase 3 study in people with these mutations," said Jeffrey Chodakewitz, M.D., Senior Vice President and Chief Medical Officer at Vertex. "While this was a small proof-of-concept study, these data are another step forward in our commitment to expand the number of people who can benefit from ivacaftor."

About the Phase 2 Study

The first part of the study included two randomized, double-blind, placebo-controlled treatment cycles (part one), and the second part of the study was an eight-week open-label period (part two). In part one, patients received ivacaftor for two, two-week treatment cycles and placebo for two, two-week treatment cycles as part of a multiple within-patient crossover design. In the first treatment cycle of part one, patients received either ivacaftor or placebo for two weeks, which was immediately followed by the opposite treatment (placebo or ivacaftor) for two weeks. The treatment cycles were separated by a four-week washout period, and in the second treatment cycle of part one, patients received either ivacaftor or placebo for two weeks, immediately followed by the opposite treatment (placebo or ivacaftor) for two weeks. Part two of the study, the open-label evaluation, was separated from the second treatment cycle by a four-week washout period, and all patients received ivacaftor in this part of the study.

The primary endpoint analysis was based on part one of the study and evaluated the mean absolute change from baseline in lung function (percent predicted forced expiratory volume in one second; $PPFEV_1$) at the end of two weeks of treatment versus placebo. The study enrolled 24 people age 12 and older with a residual function mutation. All people with a residual function mutation have some functioning CFTR protein. Depending on the specific mutation, residual function mutations can result in defective CFTR proteins at the cell surface and/or a reduced number of CFTR proteins at the cell surface.

Efficacy Results

Part One: Across part one of the study, patients showed statistically significant improvements in FEV_1 at the end of treatment with ivacaftor compared to placebo. The study met its primary endpoint as evaluated using a Bayesian Hierarchical Model (BHM) analysis, which was supported by analysis using a Mixed Model for Repeated Measures (MMRM). The BHM analysis showed a mean absolute improvement in FEV_1 of 2.3 percentage points compared to placebo, with a 95 percent credible interval of 0.38 percentage points to 4.1 percentage points. Results from part one of the study reflect data from both two-week treatment cycles for ivacaftor and, separately, for placebo. The mean baseline lung function of patients in the study was 67.8 percent predicted FEV_1, with a range of 37.8 to 108.6 percent predicted. A summary of key lung function results (MMRM) from the two-week treatment cycles is provided below:

Changes Lung Function (MMRM)	**2-Week Treatment Cycles (n=24)**		
	Ivacaftor (within-group from baseline)	***Placebo (within-group from baseline)***	***Treatment Difference***
Mean Absolute Change in FEV_1	2.8 percentage points	0.6 percentage points	2.1 percentage points (p=0.004)
Mean Relative Change in FEV_1	4.9%	0.9%	4.0% (p=0.002*)

*Statistical testing for mean relative change was conducted as part of an ad-hoc analysis

Part Two: Following the second two-week treatment cycle and a four-week washout period, patients received ivacaftor in an eight-week open-label portion of the study. In the eight-week open-label portion, improvements in lung function from baseline of part two were observed, as noted below:

Change From Baseline in Lung Function at 8 Weeks	**Open-Label Period (n=21)**
	Ivacaftor (Open-Label)
Mean Absolute Change in FEV_1	4.7 percentage points (p < 0.0001*)
Mean Relative Change in FEV_1	7.8% (p=0.0001*)

*Statistical testing for mean absolute and mean relative change was conducted as part of an ad-hoc analysis

A mean decrease in sweat chloride of 15.7 mmol/L from study baseline (before administration of the first dose of study drug in part one) was observed at the end of the eight-week open-label period. The mean baseline sweat chloride level for patients entering the study was 64.7 mmol/L. Sweat chloride was not measured in part one of the study.

Safety Results: In the study, ivacaftor was generally well-tolerated, and the safety and tolerability results were consistent with those observed in prior Phase 3 studies of ivacaftor monotherapy in people with CF who have the G551D mutation. The most common adverse events in the treatment group were cough and respiratory tract infection. One serious adverse event of pulmonary exacerbation occurred more than 14 days beyond the last dose of study drug; the patient discontinued from the study and the event was considered by the investigator to be not related to treatment. An additional two patients were discontinued from the study based on non-compliance with the study protocol. Twenty-one patients entered the open-label portion of the study and completed all dosing in the study.

Next Steps

Based on these data, Vertex plans to initiate a Phase 3 study of ivacaftor in people with residual function mutations, pending discussions with regulatory authorities regarding the design of the study.

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 that aims to help the CFTR protein function more normally once it reaches the cell surface, to help hydrate and clear mucus from the airways. KALYDECO (150mg, q12h) was first approved by the U.S. Food and Drug Administration in January 2012 for use in people with CF ages 6 and older who have at least one copy of the G551D mutation and in February 2014 for use in people with CF ages 6 and older who have the following additional CFTR mutations: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P and G1349D.

KALYDECO was approved by the European Medicines Agency in July 2012, by Health Canada in November 2012 and by the

Therapeutic Goods Administration in Australia in July 2013 for use in people with CF ages 6 and older who have at least one copy of the G551D mutation in the *CFTR* gene.

Vertex retains worldwide rights to develop and commercialize KALYDECO.

INDICATION AND IMPORTANT SAFETY INFORMATION FOR KALYDECO (ivacaftor)

Ivacaftor (150 mg tablets) is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the *CFTR* gene.

In the United States only, ivacaftor is also indicated for the treatment of CF in patients age 6 and older who have one of the following mutations in the *CFTR* gene: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

Ivacaftor is not effective in patients with CF with 2 copies of the F508del mutation (F508del/F508del) in the *CFTR* gene. The safety and efficacy of ivacaftor in children with CF younger than 6 years of age have not been established.

Elevated liver enzymes (transaminases; ALT and AST) have been reported in patients receiving ivacaftor. It is recommended that ALT and AST be assessed prior to initiating ivacaftor, every 3 months during the first year of treatment, and annually thereafter. Patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the upper limit of normal. Following resolution of transaminase elevations, consider the benefits and risks of resuming ivacaftor dosing.

Use of ivacaftor with medicines that are strong CYP3A inducers, such as the antibiotics rifampin and rifabutin; seizure medications (phenobarbital, carbamazepine, or phenytoin); and the herbal supplement St. John's Wort, substantially decreases exposure of ivacaftor and may diminish effectiveness. Therefore, co-administration is not recommended.

The dose of ivacaftor must be adjusted when used concomitantly with strong and moderate CYP3A inhibitors or when used in patients with moderate or severe hepatic disease.

Ivacaftor can cause serious adverse reactions including abdominal pain and high liver enzymes in the blood. The most common side effects associated with ivacaftor include headache; upper respiratory tract infection (the common cold), including sore throat, nasal or sinus congestion, and runny nose; stomach (abdominal) pain; diarrhea; rash; and dizziness. These are not all the possible side effects of ivacaftor. A list of the adverse reactions can be found in the product labeling for each country where ivacaftor is approved. Patients should tell their healthcare providers about any side effect that bothers them or does not go away.

Please see KALYDECO U.S. Prescribing Information, EU Summary of Product Characteristics, Canadian Product Monograph, Australian Consumer Medicine Information and Product Information, Swiss Prescribing Information and Patient Information, and the New Zealand Datasheet and Consumer Medicine Information.

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 function or absence of CFTR proteins in people with CF 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 four 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 fourth paragraph of the press release, and the information provided regarding Vertex's plans to initiate a Phase 3 study of ivacaftor in patients with residual function mutations that will evaluate longer-duration treatment with ivacaftor in a greater number of patients, pending discussions with regulatory authorities. 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 registration or further development of its compounds 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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