July 18, 2017

Vertex Announces Positive Phase 1 & Phase 2 Data from Three Different Triple Combination Regimens in People with Cystic Fibrosis Who Have One F508del Mutation and One Minimal Function Mutation (F508del/Min)

-Phase 2 data showed mean absolute improvements in ppFEV$_1$ of 9.7 and 12.0 percentage points for VX-152 and VX-440, respectively, in triple combination with tezacaftor and ivacaftor in F508del/Min patients; Initial data from Phase 1 study showed mean absolute improvement in ppFEV$_1$ of 9.6 percentage points with VX-659 triple combination in F508del/Min patients-

-First data to demonstrate the potential to treat the underlying cause of CF in people with F508del/Min mutations, a severe and difficult-to-treat type of the disease-

-Initial Phase 2 data also showed mean absolute improvements in ppFEV$_1$ of 7.3 and 9.5 percentage points when VX-152 or VX-440 was added in people with two copies of the F508del mutation (F508del/F508del), who were already receiving tezacaftor and ivacaftor-

-All 3 triple combination regimens were generally well tolerated across the studies-

BOSTON--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced positive data from Phase 1 and Phase 2 studies of three different triple combination regimens in people with cystic fibrosis (CF) who have one *F508del* mutation and one minimal function mutation (*F508del*/Min). These are the first data to demonstrate the potential to treat the underlying cause of CF in these patients, who have a severe and difficult-to-treat type of the disease. Data from the Phase 2 studies in these patients showed mean absolute improvements in percent predicted forced expiratory volume in one second (ppFEV$_1$) of 9.7 and 12.0 percentage points from baseline for the triple combination regimens with VX-152 (200mg q12h) or VX-440 (600mg q12h), respectively. Initial data from a Phase 1 study showed a mean absolute improvement in ppFEV$_1$ of 9.6 percentage points from baseline for the triple combination regimen of VX-659, tezacaftor and ivacaftor in people with one *F508del* mutation and one minimal function mutation. The company also announced today initial data showing improvements in mean absolute ppFEV$_1$ of 7.3 and 9.5 percentage points when VX-152 or VX-440 was added in people with two copies of the *F508del* mutation, who were already receiving tezacaftor and ivacaftor. Vertex will host a conference call for investors today, July 18, 2017 at 5:00 p.m. EDT, to discuss these results.

The triple combination regimens were generally well tolerated across all three studies, and the majority of adverse events were mild to moderate in severity. Across the studies, the discontinuation rate due to adverse events was low.

"These safety and efficacy data are clear and compelling, indicating significant potential benefit for people with CF from each of these three different triple combination regimens," said Jeffrey Chodakewitz, M.D., Executive Vice President and Chief Medical Officer at Vertex. "We will be collecting and evaluating additional data from these and other studies and will make a decision on which regimen(s) to take forward into pivotal program(s), which we expect to begin in the first half of 2018."

Vertex has established a Steering Committee of global CF experts and clinical trial investigators to support the design, conduct and execution of the triple combination pivotal study program. This committee is co-chaired by Steven M. Rowe, M.D., M.S.P.H., 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 for Medical Research, University of Alabama at Birmingham, and Jennifer Taylor-Cousar, M.D., 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.

"Patients with minimal function mutations have been waiting for a medicine to treat the underlying cause of their disease, which makes these data showing pronounced improvements in lung function particularly important," said Dr. Rowe. "It's also encouraging to see that the addition of a next-generation corrector may lead to substantial additional benefits for patients with two copies of the *F508del* mutation, who were already receiving tezacaftor and ivacaftor."

Next Steps

Vertex has advanced four next-generation correctors in parallel with the goal of developing the best triple combination regimen or regimens for people living with CF.

Vertex has accelerated the development programs for VX-445 and VX-659. A VX-445 Phase 2 study is underway and a VX-659 Phase 2 study will begin in early August. VX-445 and VX-659 will be evaluated in triple combination with tezacaftor and ivacaftor in people with one *F508del* mutation and one minimal function mutation and will be evaluated in people with two copies of the *F508del* mutation who are already receiving tezacaftor and ivacaftor. Data from both of these Phase 2 studies are expected in early 2018.

Pending additional data from these Phase 2 studies and the ongoing studies of VX-152 and VX-440 and discussions with regulatory agencies and the Steering Committee, Vertex plans to initiate pivotal development of one or more triple combination regimens in the first half of 2018.

About the VX-440 Phase 2 Study

This randomized, double-blind Phase 2 study is evaluating VX-440 (200mg and 600mg q12h) in combination with tezacaftor and ivacaftor in two different groups of people with CF ages 18 and older - those who have one *F508del* mutation and one minimal function mutation, and in those who have two copies of the *F508del* mutation. Minimal function mutations are those that result in little-to-no functioning CFTR protein and are not responsive to ivacaftor, tezacaftor or the combination of ivacaftor and tezacaftor. The primary objectives for the study are safety, tolerability and efficacy as assessed by mean absolute change in ppFEV$_1$ from baseline. Secondary endpoints include change in sweat chloride and Cystic Fibrosis Questionnaire-Revised (CFQ-R).

Overall Safety Data: In the study, the triple combination regimen was generally well tolerated. The majority of adverse events were mild or moderate. The most common adverse events (> 10%), regardless of treatment group, were infective pulmonary exacerbation, cough, sputum increased and diarrhea. There was one discontinuation due to an adverse event in the triple combination treatment groups (elevated liver enzymes > 5x upper limit of normal in the VX-440 600mg group) and one in the control groups (respiration abnormal and sputum increased). One additional patient treated with the triple combination had elevated liver enzymes (> 8x upper limit of normal in the VX-440 600mg group), which were observed on the final day of dosing. In both patients, the elevated liver enzymes returned to normal after treatment discontinuation or completion.

4-Week Efficacy Data in *F508del*/Min Patients: Part 1 of the study evaluated the triple combination for four weeks in 47 patients who have one *F508del* mutation and one minimal function mutation (11 in placebo, 18 in VX-440 200mg and 18 in VX-440 600mg). A summary of the within-group lung function and sweat chloride data is provided below:

VX-440 in *F508del*/Min Patients		
Mean Absolute Within-Group Change From Baseline Through Day 29*	**Mean Absolute Within-Group Change in ppFEV$_1$ (percentage points)**	**Mean Absolute Within-Group Change in Sweat Chloride (mmol/L)**
Triple placebo	+1.4 (p=0.4908)	+1.6 (p=0.6800)
VX-440 (200mg q12h) + tezacaftor (50mg q12h or 100mg QD) + ivacaftor (150mg q12h)	+10.0 (p < 0.0001)	-20.7 (p < 0.0001)
VX-440 (600mg q12h) + tezacaftor (50mg q12h) + ivacaftor (300mg q12h)	+12.0 (p < 0.0001)	-33.1 (p < 0.0001)

** all p-values are within group p-values based on mixed effect models; values expressed as 'Through Day 29' are the average of Day 15 and Day 29 measures*

A secondary endpoint in the study measured mean absolute change in the respiratory domain of CFQ-R, a validated patient-reported outcome tool, at Day 29. In this study, the mean absolute improvements for patients with a minimal function mutation who received the triple combination were 18.3 points (VX-440 200mg) and 20.7 points (VX-440 600mg). The improvement for those who received placebo was 2.2 points.

4-Week Efficacy Data in *F508del*/*F508del* Patients: Part 2 of the study is ongoing to evaluate the addition of VX-440 for four weeks in 26 patients who have two copies of the *F508del* mutation, who were already receiving the combination of

tezacaftor and ivacaftor (6 in placebo and 20 in VX-440 600mg). In this part of the study, all participants received four weeks of treatment with tezacaftor and ivacaftor and were then randomized to the addition of VX-440 or placebo for four additional weeks. A summary of the within-group lung function and sweat chloride data for the triple combination treatment period, from baseline (end of the 4-week tezacaftor/ivacaftor run-in period), is provided below:

VX-440 in *F508del*/*F508del* Patients		
Mean Absolute Within-Group Change From Baseline Through Day 29*	**Mean Absolute Within-Group Change in ppFEV$_1$ (percentage points)**	**Mean Absolute Within-Group Change in Sweat Chloride (mmol/L)**
Placebo + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	-2.5 (p=0.2755)	+2.1 (p=0.7385)
VX-440 (600mg q12h) + tezacaftor (50mg q12h) + ivacaftor (300mg q12h)	+9.5 (p < 0.0001)	-31.3 (p < 0.0001)
** all p-values are within group p-values based on mixed effect models; values expressed as 'Through Day 29' are the average of Day 15 and Day 29 measures*		

The safety follow-up portion of the study in patients with two copies of the *F508del* mutation is ongoing.

About the VX-152 Phase 2 Study

This ongoing Phase 2 randomized, double-blind study is evaluating VX-152 (100mg, 200mg and 300mg q12h) in combination with tezacaftor and ivacaftor in people with CF ages 18 and older who have one *F508del* mutation and one minimal function mutation and in people who have two copies of the *F508del* mutation. The primary objective is safety and tolerability. Secondary endpoints include mean absolute change in ppFEV$_1$ and change in sweat chloride. Data reported today are from the 100mg and 200mg arms of the study in people who have one *F508del* mutation and one minimal function mutation and from the 200mg arm in people who have two copies of the *F508del* mutation.

Overall Safety Data: In the study, the triple combination regimen was generally well tolerated. The majority of adverse events were mild or moderate. The most common adverse events (> 10%), regardless of treatment group, were cough, sputum increased, infective pulmonary exacerbation, productive cough, diarrhea and fatigue. There was one discontinuation due to an adverse event in the triple combination treatment groups (pneumonia in the VX-152 200mg group) and none in the control groups.

2-Week Initial Efficacy Data in *F508del*/Min Patients: In Part 1 of the study, the triple combination was evaluated for two weeks in 21 patients ages 18 and older who have one *F508del* mutation and one minimal function mutation (5 in combined placebo, 6 in VX-152 100mg and 10 in VX-152 200mg). A summary of the initial within-group lung function and sweat chloride data (secondary endpoints) from the VX-152 100mg and 200mg dose groups is provided below:

VX-152 in *F508del*/Min Patients		
Observed Mean Absolute Within-Group Change from Baseline at Day 15*	**Observed Mean Absolute Within-Group Change in ppFEV$_1$ (percentage points)**	**Observed Mean Absolute Within-Group Change in Sweat Chloride (mmol/L)**
Triple placebo	-0.9 (p=0.6245)	+1.0 (p=0.5659)
VX-152 (100mg q12h) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+5.6 (p=0.0135)	-19.6 (p=0.0004)
VX-152 (200mg q12h) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+9.7 (p=0.0017)	-14.1 (p=0.0219)
** p-values presented are within-group p-values based on 1 sample t-test; an efficacy analysis using mixed effect models will be conducted following completion of an additional cohort of patients currently being treated in the study*		

This part of the study is ongoing to evaluate the triple combination of VX-152 (300mg q12h), tezacaftor and ivacaftor in patients with one *F508del* mutation and one minimal function mutation. These data are expected later in 2017.

2-Week Initial Efficacy Data in *F508del*/*F508del* Patients: Part 2 of the study is ongoing to evaluate the addition of VX-152 for two weeks in 14 patients ages 18 and older who have two copies of the *F508del* mutation, who were already

receiving the combination of tezacaftor and ivacaftor (4 in placebo and 10 in VX-152 200mg). A summary of the initial within-group lung function and sweat chloride data (secondary endpoints) for the triple combination treatment period, from baseline (end of the 4-week tezacaftor/ivacaftor run-in period), is provided below:

VX-152 in *F508del/F508del* Patients		
Observed Mean Absolute Within-Group Change from Baseline at Day 15*	**Observed Mean Absolute Within-Group Change in ppFEV$_1$ (percentage points)**	**Observed Mean Absolute Within-Group Change in Sweat Chloride (mmol/L)**
Placebo + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	-1.4 (p=0.2773)	+3.4 (p=0.1212)
VX-152 (200mg q12h) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+7.3 (p=0.0354)	-20.9 (p=0.0010)
** p-values presented are within-group p-values based on 1 sample t-test; an efficacy analysis using mixed effect models will be conducted following completion of an additional cohort of patients currently being treated in the study*		

This part of the study is ongoing to evaluate the addition of VX-152 (300mg q12h) for four weeks in patients with two *F508del* mutations, who are already receiving the combination of tezacaftor and ivacaftor. These data are expected in early 2018.

About the VX-659 Phase 1 Study

This Phase 1 randomized, double-blind, placebo-controlled study evaluated the safety and tolerability of single and multiple ascending doses of VX-659 alone and in triple combination with tezacaftor and ivacaftor in healthy volunteers. It also evaluated the safety and tolerability of VX-659 as part of a triple combination for two weeks in 12 people with CF ages 18 and older who have one *F508del* mutation and one minimal function mutation (3 in placebo and 9 in VX-659 120mg). In this part of the study, sweat chloride was evaluated as an additional endpoint, and the absolute change in ppFEV$_1$ was evaluated as part of the safety analysis.

In CF patients, VX-659 was generally well tolerated in triple combination with tezacaftor and ivacaftor. The majority of adverse events were mild or moderate. The most common adverse events (> 10%), regardless of treatment group, were cough, infective pulmonary exacerbation and productive cough. There were no discontinuations due to adverse events in either group.

At Day 15, there was a mean absolute improvement in ppFEV$_1$ of +9.6 percentage points from baseline in those receiving the triple combination regimen of VX-659 (120mg q12h), tezacaftor and ivacaftor and a mean decrease in sweat chloride of -41.6 mmol/L. For those receiving placebo, there was a mean absolute decrease in ppFEV$_1$ of -0.4 percentage points and a mean decrease in sweat chloride of -11.0 mmol/L.

Preclinical Toxicology Data

In the Phase 2 study of VX-440, women of childbearing potential were required to use pre-specified, non-hormonal methods of contraception based on results from previous preclinical reproductive toxicology studies. Preclinical reproductive toxicology studies of VX-152, VX-659 and VX-445 are complete with no adverse findings of note.

About CF

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 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.

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 seven 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.

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, VX-659 and VX-445 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, Dr. Chodakewitz's statements in the third paragraph, and the information provided regarding Vertex's plans to initiate pivotal development of one or more triple combination regimens in the first half of 2018. 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, (i) that Vertex could experience unforeseen delays in conducting its development programs relating to triple combination treatments and in submitting related regulatory filings, (ii) that the initial results set forth in this press release may differ from the final results from these ongoing studies, (iii) that regulatory authorities may not approve, or approve on a timely basis, triple combination treatments due to safety, efficacy or other reasons, and (iv) 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.

(VRTX-GEN)

Conference Call and Webcast

The company will host a conference call and webcast today at 5:00 p.m. EDT to discuss these results. To access the call, please dial (866) 501-1537 (U.S.) or +1 (720) 545-0001 (International). The conference call will be webcast live, and a link to the webcast may be accessed through Vertex's website at www.vrtx.com in the "Investors" section under "Events and Presentations." To ensure a timely connection, it is recommended that users register at least 10 minutes prior to the scheduled webcast. An archived webcast will be available on the company's website.

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