Vertex Initiates Phase 3 Studies of VX-445, Tezacaftor and Ivacaftor as a Triple Combination Regimen for People with Cystic Fibrosis

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-VX-445 triple combination regimen is the second of two different triple combination regimens to enter Phase 3 development in 2018-

-Phase 3 study in approximately 360 patients with one F508del mutation and one minimal function mutation designed to support New Drug Application based on 4-week primary efficacy endpoint and 12-week safety data-

-Phase 3 study in approximately 100 patients with two F508del mutations supported by new Phase 2 data announced today that showed an incremental mean absolute improvement in ppFEV$_1$ of 11.0 percentage points when VX-445 was added in patients already receiving tezacaftor and ivacaftor; triple combination regimen was generally well tolerated-

-Additional dose-ranging of once-daily potentiator VX-561 to be conducted to support potential late-stage development of future once-daily triple combination regimens-

BOSTON--(BUSINESS WIRE)--Apr. 26, 2018-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced that it is initiating two Phase 3 studies of VX-445, tezacaftor and ivacaftor as an investigational triple combination regimen for people with cystic fibrosis (CF). The first Phase 3 study will evaluate approximately 360 people with CF who have one copy of the *F508del* mutation and one minimal function mutation and is designed to support the submission of a New Drug Application (NDA) in the U.S. using data from the study's 4-week primary efficacy endpoint together with safety data through 12 weeks of treatment. The second Phase 3 study will evaluate approximately 100 people with CF who have two copies of the *F508del* mutation, the most common genetic form of the disease, and is designed to support the submission of an application for approval in patients with two copies of the *F508del* mutation in the U.S. using data from the study's 4-week primary efficacy endpoint together with 24-week safety data generated from the Phase 3 study in patients with one *F508del* mutation and one minimal function mutation. The initiation of the study in people with two copies of the *F508del* mutation is supported by data announced today from a Phase 2 study that showed an incremental mean absolute improvement in percent predicted forced expiratory volume in one second (ppFEV$_1$) of 11.0 percentage points from baseline through week four of treatment when VX-445 (200 mg) was added in people with CF who have two *F508del* mutations and were already receiving tezacaftor in combination with ivacaftor. In the Phase 2 study, the VX-445 triple combination regimen was generally well tolerated, and the majority of adverse events were mild to moderate in severity.

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"The initiation of pivotal development for VX-445 marks important progress toward our goal of advancing two different next-generation triple combination regimens into pivotal development to allow us to bring the best regimen to people with CF," said Jeffrey Leiden, M.D., Ph.D., Chairman, President and Chief Executive Officer of Vertex. "We recognize that many people with CF are awaiting the first treatment for the underlying cause of their disease, and I am pleased that we have been able to advance both VX-659 and VX-445 into pivotal studies. We look forward to the rapid progression of these and other studies over the coming year, including studies in people currently eligible for our approved medicines where a triple combination regimen may provide significant benefit."

Vertex also today announced safety and efficacy results for the once-daily potentiator, VX-561, when dosed as part of a triple combination regimen with a next-generation corrector (VX-659 or VX-445) and tezacaftor in Phase 2 studies of people with one *F508del* mutation and one minimal function mutation. In these studies, mean absolute improvements in ppFEV$_1$ of 12.2 and 11.7 and percentage points from baseline through week four of treatment were observed for the VX-659 and VX-445 triple combination regimens, respectively. The once-daily triple combination regimens were generally well tolerated, and the majority of adverse events were mild to moderate in severity. Following discussions with the U.S. Food and Drug Administration (FDA), Vertex plans to conduct additional dose-ranging for VX-561 to support potential late-stage development of future once-daily triple combination regimens.

About the VX-445 Phase 3 Study in People with One *F508del* Mutation and One Minimal Function Mutation
The randomized, double-blind, placebo-controlled Phase 3 study will evaluate VX-445 in combination with tezacaftor and ivacaftor, or triple placebo, in approximately 360 patients ages 12 and older who have one *F508del* mutation and one minimal function mutation. A list of the minimal function mutations currently included in this study can be found here. The primary endpoint of the study is the mean absolute change in lung function (ppFEV$_1$) from baseline at week four of triple combination treatment compared

to triple placebo.

The study is designed to support the submission of an NDA to the U.S. FDA based on data from the 4-week primary efficacy analysis and on safety data through 12 weeks of treatment. The study will evaluate VX-445 in combination with tezacaftor and ivacaftor for a total of 24 weeks of treatment to generate additional safety data and data for key secondary endpoints, including the number of pulmonary exacerbations, change in body mass index, change in sweat chloride, and change in patient-reported outcomes as measured by the respiratory domain score of the Cystic Fibrosis Questionnaire-Revised (CFQ-R), among others. Data from this study will also be used to support planned regulatory submissions in Europe and other regions.

The study will evaluate a fixed-dose combination of VX-445 (200 mg), tezacaftor (100 mg) and ivacaftor (150 mg) in the morning followed by ivacaftor (150 mg) in the evening. An open-label extension study will be conducted where all eligible patients, including those who received triple placebo, will receive the VX-445 triple combination regimen for up to an additional 96 weeks.

About the VX-445 Phase 3 Study in People with Two *F508del* Mutations
The randomized, double-blind, controlled Phase 3 study will evaluate four weeks of treatment with VX-445 or placebo in combination with tezacaftor and ivacaftor in approximately 100 patients ages 12 years or older who have two *F508del* mutations. All patients will receive tezacaftor in combination with ivacaftor during a 4-week run-in prior to the start of the triple combination treatment period. The primary endpoint of the study is the mean absolute change in lung function ($ppFEV_1$) from baseline (end of the 4-week tezacaftor/ivacaftor run-in) at week four of treatment with VX-445 in combination with tezacaftor and ivacaftor compared to those who received placebo, tezacaftor and ivacaftor. Key secondary endpoints will also be measured at week four and include change in sweat chloride and change in patient-reported outcomes as measured by the CFQ-R respiratory domain score.

The study is designed to support an application for U.S. FDA approval of the VX-445 triple combination regimen in patients with two copies of the *F508del* mutation based on data from the 4-week primary efficacy analysis and secondary safety analysis and on 24-week safety data from the Phase 3 study in patients with one *F508del* mutation and one minimal function mutation. Vertex plans to use the study in patients with two *F508del* mutations to broaden the potential label for the VX-445 triple combination regimen and does not anticipate that the study will impact its initial planned submission of an NDA to the U.S. FDA for patients with one *F508del* mutation and one minimal function mutation. Data from the study in patients with two *F508del* mutations will also be used to support planned regulatory submissions in Europe and other regions.

The study will evaluate a fixed-dose combination of VX-445 (200 mg) with tezacaftor (100 mg) and ivacaftor (150 mg) in the morning followed by ivacaftor (150 mg) in the evening, which is the same dosing regimen being evaluated in the Phase 3 study of patients with one *F508del* mutation and one minimal function mutation. An open-label extension study will be conducted where all eligible patients, including those who received placebo, tezacaftor and ivacaftor, will receive the VX-445 triple combination regimen for up to an additional 96 weeks.

Phase 2 Data for VX-445 Triple Combination in People with Two *F508del* Mutations
The initiation of the Phase 3 study in people with two *F508del* mutations is supported by data announced today from a randomized, double-blind, controlled Phase 2 study where the primary objectives were safety, tolerability and efficacy as assessed by mean absolute change in $ppFEV_1$ from baseline (end of the 4-week tezacaftor/ivacaftor run-in period) through week four of treatment. Secondary endpoints included absolute change in sweat chloride and change in the CFQ-R respiratory domain score.

All patients received a 4-week run-in of tezacaftor in combination with ivacaftor. Patients were then randomized to add either once-daily VX-445 (200 mg) or placebo to tezacaftor and ivacaftor for four weeks. After the 4-week triple combination dosing period, all patients received four weeks of tezacaftor and ivacaftor, followed by a 4-week safety follow-up period.

Safety Data: The triple combination regimen was generally well tolerated, and the safety profile was similar to that observed in previously reported parts of this study. The majority of adverse events were mild or moderate. No serious adverse events were reported in the triple combination group and one serious adverse event (pulmonary exacerbation) was reported in the group that received placebo added to tezacaftor and ivacaftor. The most common adverse events occurring in at least two patients in any treatment group were sputum increased, cough, infective pulmonary exacerbation, fatigue, pyrexia, AST increased, CPK increased, chills, hemoptysis, ALT increased, respiration abnormal and sputum discolored. There was one discontinuation in the triple combination group due to chest pain, and one patient interrupted then discontinued treatment in the group that received placebo added to tezacaftor and ivacaftor due to increased bilirubin without associated elevations in transaminases. Following treatment discontinuation, the chest pain resolved and the increased bilirubin returned to baseline. One patient in the triple combination group interrupted treatment in the tezacaftor/ivacaftor treatment period that followed triple combination dosing due to myopathy and increased CPK, ALT and AST. The events resolved following interruption of treatment, and the patient subsequently restarted and completed treatment in the tezacaftor/ivacaftor period without any further incidence.

Efficacy Data: A summary of the within-group lung function and sweat chloride data is provided below:

VX-445 Added to Ongoing Treatment with Tezacaftor and Ivacaftor in Patients with Two *F508del* Mutations

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 (100 mg QD) + ivacaftor (150 mg q12h) (n=7)	+0.4 (p=0.8869)	+0.8 (p=0.8712)
VX-445 (200 mg QD) + tezacaftor (100 mg QD) + ivacaftor (150 mg q12h) (n=21)	+11.0 (p<0.0001)	-39.6 (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; baseline reflects the end of the 4-week tezacaftor/ivacaftor run-in period*

A secondary endpoint in the study measured mean absolute within-group change in the respiratory domain score of the CFQ-R[1], a validated patient-reported outcome measure, at Day 29. The mean absolute improvement for patients who received VX-445 in addition to tezacaftor and ivacaftor was 20.7 points. The improvement for those who received placebo in addition to tezacaftor and ivacaftor was 5.2 points.

Once-daily Triple Combination Regimens

Vertex today announced the first safety and efficacy results for once-daily triple combination regimens that included a next-generation corrector (VX-659 or VX-445), tezacaftor and VX-561, a once-daily potentiator, in patients with one *F508del* mutation and one minimal function mutation. These once-daily regimens were evaluated as separate parts within the Phase 2 studies for VX-659 and VX-445, and safety and efficacy data from previously completed parts of these studies in patients with one *F508del* mutation and one minimal function mutation were reported earlier in 2018. The primary objectives of the studies were safety, tolerability and efficacy as assessed by mean absolute change in $ppFEV_1$ from baseline through week four of treatment. Secondary endpoints included change in sweat chloride and change in the CFQ-R respiratory domain score.

VX-659 Once-daily Regimen

Safety Data: In this study, the once-daily triple combination regimen of VX-659, tezacaftor and VX-561 was generally well tolerated, and the safety profile was similar to that observed in previously reported parts of this study that evaluated VX-659, tezacaftor and ivacaftor. The majority of adverse events were mild or moderate. Serious adverse events were reported in three patients in the placebo group (infective pulmonary exacerbations) and two in the triple combination group (1 with pyrexia, dyspnea and pleuritic pain, and 1 with infective pulmonary exacerbation and pneumonia). None of these serious adverse events were considered related to treatment and none resulted in treatment discontinuation. The most common adverse events occurring in at least two patients in any treatment group were cough, infective pulmonary exacerbation, nausea, oropharyngeal (throat) pain, pyrexia, rales and rash. One patient in the triple combination group interrupted treatment for rash and subsequently restarted then discontinued treatment for drug hypersensitivity, which resolved after treatment discontinuation. A second patient in the triple combination treatment group interrupted treatment for rash. The rash resolved, and the patient restarted and completed triple combination treatment without any further incidence.

Efficacy Data: A summary of the within-group lung function and sweat chloride data is provided below:

Once-daily VX-659, tezacaftor and VX-561 in Patients with one *F508del* Mutation and One Minimal Function Mutation

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 (n=6)	-5.0 (p=0.1561)	-1.3 (p=0.8077)
VX-659 (400 mg QD) + tezacaftor (100 mg QD) + VX-561 (200 mg QD) (n=19)	+12.2 (p<0.0001)	-38.1 (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 within-group change in the respiratory domain score of the CFQ-R[1] at Day 29. The mean absolute improvement for patients who received the triple combination was 14.7 points. The change for those who received placebo was -4.1 points.

VX-445 Once-daily Regimen

Safety Data: In this study, the once-daily triple combination regimen of VX-445, tezacaftor and VX-561 was generally well tolerated, and the safety profile was similar to that observed in previously reported parts of this study that evaluated VX-445, tezacaftor and ivacaftor. The majority of adverse events were mild or moderate. A serious adverse event was reported in one patient in the placebo group (infective pulmonary exacerbation), and there were no serious adverse events in the triple combination group. The most common adverse events occurring in at least two patients in any treatment group were cough, nausea, oropharyngeal (throat) pain, infective pulmonary exacerbation, nasal congestion, productive cough, sputum increased, chest pain, paranasal sinus discomfort, upper respiratory tract infection and vomiting. There was one discontinuation in the triple combination group due to rash. Following treatment discontinuation, the rash resolved.

Efficacy Data: A summary of the within-group lung function and sweat chloride data is provided below:

Once-daily VX-445, tezacaftor and VX-561 in Patients with One *F508del* Mutation and One Minimal Function Mutation

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 (n=8)	+1.2 (p=0.6407)	+1.0 (p=0.8359)
VX-445 (200 mg QD) + tezacaftor (100 mg QD) + VX-561 (150 mg QD) (n=21)	+11.7 (p<0.0001)	-33.6 (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 within-group change in the respiratory domain score of the CFQ-R[1] at Day 29. The mean absolute improvement for patients who received the triple combination was 20.2 points. The improvement for those who received placebo was 20.2 points.

Following discussions with the U.S. FDA, Vertex plans to conduct additional dose-ranging with VX-561 to support potential late-stage development of future once-daily triple combination regimens.

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 invests in scientific innovation to create transformative medicines for people with serious and life-threatening diseases. In addition to clinical development programs in CF, Vertex has more than a dozen ongoing research programs focused on the underlying mechanisms of other serious diseases.

Founded in 1989 in Cambridge, Mass., Vertex's headquarters is now located in Boston'sInnovation District. Today, the company has research and development sites and commercial offices in the United States, Europe, Canada and Australia. Vertex is consistently recognized as one of the industry's top places to work, including being named to *Science* magazine's Top Employers in the life sciences ranking for eight years in a row. 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), SYMDEKO ™ (tezacaftor/ivacaftor and ivacaftor), 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. Leiden's statements in the second paragraph and the information provided regarding (i) the timing and design of the Phase 3 studies of VX-445 in combination with tezacaftor and ivacaftor, (ii) the potential to submit approval applications to the FDA based on data from these Phase 3 studies, (iii) potential to support planned regulatory submissions in Europe and other regions with data from these Phase 3 studies and (iv) plans with respect to further development of VX-561. 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 that data from the Phase 3 development programs may not support continued development or approval of the company's triple-combination regimens 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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[1] CFQ-R results reported are based on a mixed effect model not adjusted for baseline CFQ-R

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