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Vertex Selects Two Next-Generation Correctors, VX-659 and VX-445, to Advance into Phase 3 Development as Part of Two Different Triple Combination Regimens for People with Cystic Fibrosis

- Phase 2 data showed mean absolute improvements in ppFEV$_1$ of up to 13.3 and 13.8 percentage points for VX-659 and VX-445, respectively, in triple combination with tezacaftor and ivacaftor in people with CF who have one F508del mutation and one minimal function mutation (F508del/Min); triple combination regimens were generally well tolerated across the studies -

- Regulatory discussions ongoing to finalize design of Phase 3 programs; first program to begin in first half of 2018 -

NOTE: In the prior version of this press release, the dose of tezacaftor was indicated as "q12h" in two places. The dose of tezacaftor used in all dose arms was "QD" and the release has been updated accordingly.

BOSTON--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced the selection of two next-generation correctors, VX-659 and VX-445, to advance into Phase 3 development as part of two different triple combination regimens for people with cystic fibrosis (CF). The decision to advance VX-659 and VX-445 into Phase 3 development was based on initial Phase 2 data, including new data from ongoing Phase 2 studies that showed mean absolute improvements in percent predicted forced expiratory volume in one second (ppFEV$_1$) of up to 13.3 and 13.8 percentage points from baseline through four weeks of treatment for the triple combination regimens with VX-659 (400mg QD) or VX-445 (200mg QD), respectively, in people who have one *F508del* mutation and one minimal function mutation (*F508del*/Min). Regulatory discussions are ongoing to finalize the design of Phase 3 programs for VX-659 and VX-445. Upon completion of these discussions, Vertex plans to initiate a Phase 3 program in the first half of 2018 to evaluate VX-659 in triple combination with tezacaftor and ivacaftor. In addition, the company plans to initiate a Phase 3 program in mid-2018 to evaluate VX-445 in triple combination with tezacaftor and VX-561 as a once-daily regimen, pending additional data in the first half of 2018, including the Phase 2 data on the combination of VX-445, tezacaftor and VX-561. Vertex will discuss the Phase 2 data and Phase 3 development strategy during the company's fourth-quarter and full-year 2017 financial results call for investors today, January 31, 2018 at 4:30 p.m. ET.

The triple combination regimens were generally well tolerated across both 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 results support the selection of both the VX-659 and VX-445 triple combination regimens and underscore the potential for these regimens to provide significant clinical benefits for up to 90 percent of people with CF," said Jeffrey Chodakewitz, M.D., Executive Vice President and Chief Medical Officer at Vertex. "We look forward to concluding our discussions with regulators and initiating Phase 3 development in the first half of the year, with the goal of bringing a triple combination regimen to patients as quickly as possible."

"The triple combination data demonstrate the rapid advances we are making in treating the underlying cause of CF," said Jennifer Taylor-Cousar, M.D., M.S.C.S., Associate Professor of Medicine and Pediatrics at National Jewish Health, Colorado, and co-chair of Vertex's Triple Combination Steering Committee. "Together, all the Phase 2 data to date provide further evidence that the addition of a next-generation corrector to tezacaftor and ivacaftor has the potential to provide substantial clinical benefits to patients with one *F508del* and one minimal function mutation who don't currently have a medicine to treat the underlying cause of their CF, as well as to provide additional benefits to patients with at least one *F508del* mutation who are already eligible for CFTR modulator therapies."

About the Phase 3 Programs

Vertex is in the process of finalizing Phase 3 study designs for VX-659 and VX-445 with regulatory agencies, with the goal of bringing a potential triple combination regimen to patients as quickly as possible. Upon completion of these discussions, the company plans to begin the first Phase 3 program in the first half of 2018, which will initially evaluate VX-659 in triple combination with tezacaftor and ivacaftor in *F508del*/Min patients. A second study, also to begin in the first half of 2018, will evaluate this triple combination in people with two copies of the *F508del* mutation (*F508del*/*F508del*). Pending data from the ongoing Phase 2 study and completion of regulatory discussions, Vertex plans to initiate a Phase 3 program in mid-2018 to

evaluate VX-445 with tezacaftor and VX-561 as a once-daily regimen in *F508del*/Min and *F508del*/*F508del* patients.

The VX-659 and VX-445 Phase 2 studies are both ongoing to evaluate triple combination regimens with tezacaftor and ivacaftor in *F508del*/*F508del* patients and triple combination regimens with tezacaftor and VX-561 as a once-daily regimen in *F508del*/Min patients. Vertex expects these data in the first half of 2018.

The decision to advance VX-659 and VX-445 into Phase 3 development was based on initial data from the Phase 2 studies of the company's four next-generation correctors - VX-659, VX-445, VX-152 and VX-440, each in triple combination with tezacaftor and ivacaftor. Initial data from the ongoing VX-659 and VX-445 studies were announced today and are below. In July 2017, Vertex reported results from the VX-440 study as well as results from the 100mg and 200mg arms of the VX-152 study.

About the VX-659 Phase 2 Study

This ongoing randomized, double-blind Phase 2 study is evaluating VX-659 (80mg, 240mg and 400mg QD) 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 (Part 1), and in those who have two copies of the *F508del* mutation (Part 2). 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 tezacaftor and ivacaftor. Part 3 of the study is evaluating VX-659 in combination with tezacaftor and VX-561 as a potential once-daily triple combination regimen in *F508del*/Min patients. The primary objectives of 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). Data reported today are from Part 1 of the study. Parts 2 and 3 of the study are ongoing with data expected in the first half of 2018.

Safety Data: In Part 1 of the study, the triple combination regimen was generally well tolerated. The majority of adverse events were mild or moderate. Serious adverse events were reported in seven patients: three patients in the placebo group (2 with infective pulmonary exacerbations and 1 with decreased pulmonary function test) and four in the triple combination groups (3 with infective pulmonary exacerbations and 1 with influenza). None of these serious adverse events were considered related to treatment and none resulted in treatment discontinuation. The most common adverse events (> 10%), regardless of treatment group, were cough, headache, oropharyngeal (throat) pain and sputum increased. There were no discontinuations due to adverse events. One patient interrupted treatment due to an adverse event in the triple combination treatment groups (rash). The rash resolved following interruption of treatment and the patient subsequently restarted and completed triple combination treatment without any further incidence.

Efficacy Data: Part 1 of the study evaluated the triple combination for four weeks in 63 patients who have one *F508del* mutation and one minimal function mutation (10 in placebo, 11 in VX-659 80mg, 20 in VX-659 240mg and 22 in VX-659 400mg). A summary of the within-group lung function and sweat chloride data is provided below:

VX-659 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	+0.3 (p=0.9053)	+2.9 (p=0.5338)
VX-659 (80mg QD) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+10.2 (p=0.0004)	-45.8 (p < 0.0001)
VX-659 (240mg QD) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+11.6 (p < 0.0001)	-43.7 (p < 0.0001)
VX-659 (400mg QD) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+13.3 (p < 0.0001)	-51.4 (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,[1] a validated patient-reported outcome measure, at Day 29. The mean absolute improvements for patients who received the triple combination were 24.6 points (VX-659 80mg), 19.8 points (VX-659 240mg) and 21.8 points (VX-659 400mg). The improvement for those who received placebo was 4.7 points.

About the VX-445 Phase 2 Study

This ongoing Phase 2 randomized, double-blind study evaluated the safety and tolerability of single and multiple ascending doses of VX-445 alone and in triple combination with tezacaftor and ivacaftor in healthy volunteers (Parts A, B and C). It is also evaluating the safety, tolerability and efficacy of VX-445 (50mg, 100mg and 200mg QD) in triple combination with tezacaftor and ivacaftor for four weeks in people with CF ages 18 and older who have one *F508del* mutation and one minimal function mutation (Part D) and in people who have two copies of the *F508del* mutation (Part E). Part F of the study is evaluating VX-445 in combination with tezacaftor and VX-561 as a potential once-daily triple combination regimen in *F508del*/Min patients. The primary objectives of the parts of the study in CF patients are safety, tolerability and efficacy as assessed by mean absolute change in $ppFEV_1$ from baseline. Secondary endpoints include change in sweat chloride and CFQ-R. Data reported today are from Part D of the study. Parts E and F of the study are ongoing with data expected in the first half of 2018.

Safety Data: In Part D of the study, the triple combination regimen was generally well tolerated. The majority of adverse events were mild or moderate. Serious adverse events were reported in five patients: two patients in the placebo group (1 with hemoptysis and 1 with infective pulmonary exacerbation) and three patients in the triple combination groups (1 patient with infective pulmonary exacerbation, jugular vein thrombosis related to a central line, and distal intestinal obstruction syndrome; 1 patient with infective pulmonary exacerbation and influenza; and 1 patient with infective pulmonary exacerbation). None of these serious adverse events were considered related to treatment and none resulted in treatment discontinuation. The most common adverse events (> 10%), regardless of treatment group, were cough, sputum increased, infective pulmonary exacerbation, hemoptysis, headache, nasal congestion, nausea, oropharyngeal pain and pyrexia. Two patients discontinued treatment due to adverse events in the triple combination treatment groups (1 patient with rash and 1 patient with increased bilirubin without associated elevations in transaminases) and none in the placebo group. Following treatment discontinuation, the rash resolved and the increased bilirubin returned to baseline. Two patients interrupted treatment due to adverse events in the triple combination groups (1 with constipation and 1 with increased bilirubin without associated elevations in transaminases); both events resolved when treatment was interrupted and both patients subsequently restarted and completed triple combination treatment without further incident.

Efficacy Data: Part D of the study evaluated the triple combination for four weeks in 65 patients who have one *F508del* mutation and one minimal function mutation (12 in combined placebo, 10 in VX-445 50mg, 22 in VX-445 100mg and 21 in VX-445 200mg). A summary of the within-group lung function and sweat chloride data is provided below:

VX-445 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	0.0 (p=0.9943)	-2.2 (p=0.5804)
VX-445 (50mg QD) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+11.1 (p < 0.0001)	-38.2 (p < 0.0001)
VX-445 (100mg QD) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+7.8 (p < 0.0001)	-33.2 (p < 0.0001)
VX-445 (200mg QD) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+13.8 (p < 0.0001)	-39.1 (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 at Day 29. The mean absolute improvements for patients who received the triple combination were 20.8 points (VX-445 50mg), 15.4 points (VX-445 100mg) and 25.7 points (VX-445 200mg). The improvement for those who received placebo was 4.2 points.

About the VX-152 Phase 2 Study

In July 2017, Vertex reported results for the 100mg and 200mg dose arms of the ongoing VX-152 Phase 2 study, which was also evaluating a 300mg dose of VX-152 in combination with tezacaftor and ivacaftor for two weeks in people who have one *F508del* mutation and one minimal function mutation and for four weeks in people who have two copies of the *F508del* mutation. Results from the 300mg arms of the VX-152 study were consistent with previously reported results, which showed a favorable safety profile, and rapid and significant increases in $ppFEV_1$.

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's Innovation 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), 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 and Dr. Taylor-Cousar's statements in the third and fourth paragraphs, respectively, and the information provided regarding (i) Vertex's selection of VX-659 and VX-445, (ii) additional data Vertex expects from its ongoing Phase 2 next-generation clinical trials, (iii) Vertex's regulatory discussions to finalize the design of the Phase 3 development programs and (iv) the timing and design of Vertex's Phase 3 development programs for VX-659 and VX-445. 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: (i) that Vertex could experience unforeseen delays in initiating its Phase 3 development programs to evaluate VX-659 and/or VX-445 as part of triple combination regimens, (ii) that the data set forth in this press release from the ongoing Phase 2 clinical trials may differ from data from additional parts of these Phase 2 clinical trials, (iii) that data from the Phase 3 development programs may not support approval of the company's triple-combination regimens due to safety, efficacy or other reasons, and (iv) 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)

[1] CFQ-R results reported are based on a mixed effect model not adjusted for baseline CFQ-R

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