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Treatment with VX-661 and Ivacaftor in a Phase 2 Study Resulted in Statistically Significant Improvements in Lung Function in People with Cystic Fibrosis Who Have Two Copies of the F508del Mutation

-Treatment with combination of VX-661 and ivacaftor for 28 days in two highest dose groups resulted in mean relative increases in lung function (percent predicted FEV₁) of 9.0% (p=0.01) and 7.5% (p=0.02) versus placebo -

-VX-661 was generally well-tolerated alone and in combination with ivacaftor-

-Vertex to host investor conference call at 4:30 p.m. ET today-

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced data from a Phase 2 study of VX-661 and ivacaftor that showed statistically significant improvements in lung function among adults with cystic fibrosis (CF) who have two copies (homozygous) of the most common mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, known as F508del. The study evaluated four dose levels of VX-661 (10, 30, 100 and 150 mg) dosed once daily for 28 days in combination with ivacaftor (150 mg) dosed twice daily. The study also evaluated a separate group of patients who received VX-661 (10, 30, 100 and 150 mg) dosed without ivacaftor for 28 days. Dose-dependent, mean relative improvements in lung function (percent predicted forced expiratory volume in one second; FEV₁), both within group and versus placebo, were observed across the combination dosing groups. Patients in the 100 and 150 mg combination dose groups showed statistically significant mean relative improvements in lung function, versus placebo, of 9.0 percent (p=0.01) and 7.5 percent (p=0.02), respectively, at Day 28. In contrast, patients who received placebo showed a 0.03 percent mean relative change in lung function at Day 28 (within-group). The mean relative FEV₁ across the combination dose groups returned toward baseline during the post-treatment 28-day washout period. VX-661 was generally well-tolerated, both as monotherapy and in combination with ivacaftor, and most adverse events were mild to moderate in severity and similar between the treatment groups and those who received placebo. Vertex plans to conduct additional studies of VX-661 to further evaluate its potential for late-stage development, pending regulatory discussions.

"This first study of VX-661 and ivacaftor provides further validation of the strategy of combining a corrector and potentiator to improve lung function in people with the most common type of cystic fibrosis," Peter Mueller, Ph.D., Chief Scientific Officer and Executive Vice President of Global Research and Development at Vertex. "With these data and the recent initiation of a Phase 3 program for a combination of our lead *CFTR* corrector VX-809 with ivacaftor, we are making significant progress toward our goal to help many more people with CF."

Cystic fibrosis is caused by a defective or missing *CFTR* protein resulting from mutations in the *CFTR* gene. In people with two copies of the most common mutation in the *CFTR* gene, F508del, little to no *CFTR* protein reaches the cell surface. VX-661, known as a *CFTR* corrector, is believed to help *CFTR* protein reach the cell surface. Ivacaftor, known as a *CFTR* potentiator, keeps cell surface *CFTR* protein channels open longer to increase the flow of salt and water. Worldwide, nearly half of people with CF have two copies of the F508del mutation and an additional one-third have one copy of the F508del mutation.

About the Study

The Phase 2 randomized, double-blind, placebo-controlled study treated 128 people with CF ages 18 and older with two copies of the F508del mutation. One group of patients was randomized to receive either VX-661 (10, 30, 100 and 150 mg dosed once daily), or placebo, alone for 28 days. A separate group of patients was randomized to receive the combination of VX-661 (10, 30, 100 and 150 mg dosed once daily) and ivacaftor (150 mg dosed twice daily), or placebo, for 28 days. The primary endpoints of the study were safety, tolerability and change in sweat chloride. Change in lung function (percent predicted forced expiratory volume in one second; FEV₁) was measured as a secondary endpoint.

There were statistically significant mean absolute decreases in sweat chloride, both within-group and versus placebo, across the combination and monotherapy groups. These changes were generally modest and were variable across the dose groups.

VX-661 was generally well-tolerated when dosed alone and in combination with ivacaftor. The most common adverse events were pulmonary in nature. Most adverse events were mild to moderate in severity and similar between the treatment and

placebo groups, and the types and frequency of adverse events were similar between the treatment and placebo groups. The rate of serious adverse events was also similar between the treatment groups and those who received placebo.

Lung Function Results for Combination Dosing

Mean absolute and relative improvements in lung function were observed in all the combination dosing groups (10, 30, 100 and 150 mg), both within group and versus placebo. The improvements in lung function were dose dependent, with the greatest improvements observed in the groups that received the highest doses of VX-661 in combination with ivacaftor. Patients in the two highest combination dose groups (VX-661 100 mg or 150 mg in combination with ivacaftor 150 mg) showed statistically significant mean relative improvements in lung function, versus placebo, of 9.0 percent (p=0.01) and 7.5 percent (p=0.02), respectively at Day 28. Improvements in FEV₁ were observed early in treatment, and the mean relative FEV₁ improvements, versus placebo, for the highest combination group (VX-661 150 mg in combination with ivacaftor 150 mg) were statistically significant at Days 14, 21 and 28. The mean relative FEV₁ across the combination dose groups returned toward baseline during the post-treatment 28-day washout period. Additional lung function results are noted below:

Mean Changes in Lung Function	Mean Relative Change in Percent Predicted FEV ₁ From Baseline		Mean Absolute Change in Percent Predicted FEV ₁ From Baseline	
	Day 0 - 28	28 Days Post-Treatment (Within-Group Mean)*	Day 0 - 28	28 Days Post-Treatment (Within-Group Mean)*
Placebo (n=23) (within group)	0.03 (NS)	1.6	-0.4 (NS)	0.6
Combination Treatment Arms	vs. Placebo		vs. Placebo	
VX-661 (10 mg) + ivacaftor (150 mg) (n=17)	4.1 (NS)	1.7	2.3 (NS)	0.8
VX-661 (30 mg) + ivacaftor (150 mg) (n=17)	5.4 (NS)	1.2	3.4 (NS)	0.5
VX-661 (100 mg) + ivacaftor (150 mg) (n=15)	9.0 (p=0.01)	1.7	4.8 (p=0.01)	0.5
VX-661 (150 mg) + ivacaftor (150 mg) (n=16)	7.5 (p=0.02)	1.4	4.5 (p=0.01)	0.7

NS = Not Statistically Significant

* The statistical analysis plan (SAP) for this study did not include statistical comparisons for the 28-day washout period

In the dose group that evaluated 100 mg of VX-661 in combination with ivacaftor, 66.7 percent (10/15) of patients had a 5 percent or greater relative improvement (within subject) in lung function at Day 28. In the dose group that evaluated 150 mg of VX-661 in combination with ivacaftor, 56.3 percent (9/16) of patients had a 5 percent or greater relative improvement (within subject) in lung function at Day 28. 21.7 percent (5/23) of patients who received placebo had a 5 percent or greater relative improvement (within subject) in lung function at Day 28.

Results for VX-661 Monotherapy Dosing

Mean absolute and relative increases in lung function were observed in all the VX-661 monotherapy dosing groups (10, 30, 100 and 150 mg), both within group and versus placebo at Day 28. These increases were variable, not dose-dependent and not statistically significant in any of the monotherapy dosing groups.

Mean Changes in Lung Function	Mean Relative Change in Percent Predicted FEV ₁ From Baseline	Mean Absolute Change in Percent Predicted FEV ₁ from Baseline
	Day 0 - 28	Day 0 - 28
Placebo (n=23) (within group)	0.03 (NS)	-0.4 (NS)
Monotherapy Treatment Arms (vs. placebo)		
VX-661 (10 mg) (n=7)	4.5 (NS)	3.6 (NS)
VX-661 (30 mg) (n=8)	0.1 (NS)	0.5 (NS)
VX-661 (100 mg) (n=8)	3.1 (NS)	1.9 (NS)
VX-661 (150 mg) (n=9)	4.2 (NS)	2.7 (NS)

NS = Not Statistically Significant

Advancing Multiple Correctors

Vertex has advanced three correctors from research into development - VX-809, VX-661 and VX-983. VX-809 is Vertex's lead corrector and is currently being evaluated in combination with ivacaftor as part of two ongoing Phase 3 studies expected to enroll a total of approximately 1,000 people ages 12 and older with two copies of the F508del mutation. Vertex expects to obtain 24-week safety and efficacy data from these studies and to submit a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) in 2014, pending study results. VX-661 is Vertex's second corrector to enter clinical development. Vertex plans to conduct additional studies of VX-661 to further evaluate its potential for late-stage development, pending regulatory discussions. VX-983 is the third corrector to enter clinical development and is currently being evaluated as part of a Phase 1 multiple-ascending-dose study in healthy volunteers. In the second half of 2013, Vertex plans to begin a 28-day study of VX-983 in combination with ivacaftor in people with two copies of the F508del *CFTR* mutation.

In addition to Vertex's development activities focused on combinations of a corrector with ivacaftor, the company has an active research program that has identified next-generation correctors that could be used as part of future combination regimens for people with CF.

About Cystic Fibrosis

Cystic fibrosis is a rare life-shortening genetic disease for which there is no cure. It affects approximately 30,000 people in the United States and 70,000 people worldwide. Today, the median predicted age of survival for a person with CF is approximately 37 years in the United States, but the average 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 1,800 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 proteins at the cell surface. The absence of working CFTR proteins results in poor flow of salt and water into and out of the cell in a number of organs, including the lungs.

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 non-profit drug discovery and development affiliate of the Cystic Fibrosis Foundation in the U.S. This collaboration was expanded to support the accelerated discovery and development of Vertex's CFTR modulators.

About Vertex

Vertex creates new possibilities in medicine. Our team discovers, develops and commercializes innovative therapies so people with serious diseases can lead better lives.

Vertex scientists and our collaborators are working on new medicines to cure or significantly advance the treatment of hepatitis C, cystic fibrosis, rheumatoid arthritis and other life-threatening diseases.

Founded more than 20 years ago in Cambridge, Mass., we now have ongoing worldwide research programs and sites in the U.S., U.K. and Canada. Today, Vertex has more than 2,000 employees around the world, and for three years in a row, *Science* magazine has named Vertex one of its Top Employers in the life sciences.

Conference Call Information

Vertex will host a conference call and webcast today, April 18, 2013 at 4:30 p.m. ET to review the Phase 2 results for VX-661. The conference call will be webcast live, and a link to the webcast may be accessed from the 'Vertex Events' page of Vertex's website at www.vrtx.com.

To listen to the live call on the telephone, dial 1-866-501-1537 (United States and Canada) or 1-720-545-0001 (International). To ensure a timely connection, it is recommended that users register at least 15 minutes prior to the scheduled webcast.

The conference ID number for the live call and replay is 46110587.

The call will be available for replay via telephone commencing April 18, 2013 at 8:00 p.m. ET running through 4:30 p.m. ET on April 25, 2013. The replay phone number for the United States and Canada is 1-855-859-2056. The international replay number is 1-404-537-3406.

Following the live webcast, an archived version will be available on Vertex's website until 4:30 p.m. ET on April 25, 2013. Vertex is also providing a podcast MP3 file available for download on the Vertex website at 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. Mueller's statements in the second paragraph of this press release and statements regarding (i) Vertex's plans to conduct additional studies of VX-661 to further evaluate its potential for late-stage development; (ii) Vertex's expectation that it will obtain 24-week safety and efficacy data from its Phase 3 studies of VX-809 in combination with ivacaftor and submit an NDA to the FDA in 2014, (iii) Vertex's plans to begin a 28-day study of VX-983 in combination with ivacaftor in the second half of 2013 and (iv) the possibility that next-generation correctors that Vertex has identified could be used as part of future combination regimens for people with CF. While Vertex believes the forward-looking statements contained in this press release are accurate, those statements are subject to risks and uncertainties that could cause actual outcomes to vary materially from the outcomes referenced in the forward-looking statements. These risks and uncertainties include, among other things: the Phase 3 studies of VX-809 in combination with ivacaftor and the additional studies of VX-661 in combination with ivacaftor may be prevented or delayed; the Phase 3 studies of VX-809 in combination with ivacaftor may not support registration and the additional studies of VX-661 in combination with ivacaftor may not support late-stage development due to safety, efficacy or other reasons; and the 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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