Vertex Announces Primary Endpoint Achieved in Phase 2 Study of VX-864 in Alpha-1 Antitrypsin Deficiency

June 10, 2021

- Treatment with VX-864 led to a statistically significant increase from baseline in plasma functional AAT levels as compared to placebo and was generally well tolerated -

- Results provide proof-of-mechanism, although magnitude of treatment effect observed unlikely to translate into substantial clinical benefit; VX-864 will not advance into late-stage development -

- Vertex to advance additional novel small molecule(s) with potential for greater clinical efficacy into the clinic in 2022 -

- Vertex will host an investor conference call and webcast today, Thursday, June 10 at 4:30 p.m. EDT -

BOSTON--(BUSINESS WIRE)--Jun. 10, 2021-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced that in a Phase 2 proof-of-concept study, VX-864 achieved rapid, consistent and statistically significant increases in mean functional alpha-1 antitrypsin (fAAT) levels of 2.2 to 2.3 micromolar from baseline in people with alpha-1 antitrypsin deficiency (AATD) with the PiZZ genotype, across three dose groups of VX-864 compared to placebo. VX-864 was generally well tolerated in the Phase 2 study. These data provide clear evidence that an oral small molecule corrector designed to promote the proper folding of the mutant Z-AAT protein can increase plasma levels of fAAT in patients with AATD. Although results provide proof-of-mechanism, the magnitude of treatment effect observed in this study is unlikely to translate into substantial clinical benefit. As such, Vertex will not advance VX-864 into late-stage development and instead will advance additional novel small molecule correctors with the potential for increased clinical efficacy into the clinic.

This press release features multimedia. View the full release here: https://www.businesswire.com/news/home/20210610005939/en/

“This is the first time that dosing of a small molecule corrector of the Z-AAT protein resulted in significant elevations in both functional and antigenic levels of AAT in people with AATD. We are encouraged by the clear separation of AAT levels in the VX-864 treated groups versus placebo and the favorable safety profile,” said Carmen Bozic, M.D., Executive Vice President, Global Medicines Development and Medical Affairs, and Chief Medical Officer at Vertex. “Based on these findings, we remain committed to developing transformative treatments for AATD and are working with urgency to translate the learnings from this study to optimize the next set of small molecule correctors so that we can fully realize the potential that this class of molecules may hold for people living with this disease.”

Efficacy Results

The study met its primary endpoint, with all VX-864 dose groups demonstrating highly statistically significant increases in plasma fAAT levels from baseline compared to placebo at day 28 of treatment. Treatment with VX-864 resulted in a mean increase of 2.2 to 2.3 micromolar in fAAT levels across the three dose groups studied compared to placebo. All dose groups showed a rapid increase in fAAT by day 7 which was sustained over 28 days of treatment. Similar statistically significant increases in antigenic AAT levels were observed compared to placebo, with a mean increase of 2.7 to 3.5 micromolar across the three dose groups studied. Plasma fAAT levels returned to baseline, in the 28-day safety follow-up period following VX-864 discontinuation, consistent with the half-life of native AAT protein and further confirming the biological activity of VX-864.

Figure 1: Statistically significant increase in mean functional and antigenic AAT observed at day 28 compared to placebo

	Change in **Functional AAT** from Baseline at Day 28 (micromolar)	P value vs placebo	Change in **Antigenic AAT** from Baseline at Day 28 (micromolar)	P value vs placebo
Placebo (N=7)	-0.1	-	-0.1	-
VX-864 100 mg q12h (N=10)	+2.3	<0.0001	+3.4	<0.0001
VX-864 300 mg q12h (N=9)	+2.3	<0.0001	+2.9	<0.0001
VX-864 500 mg q12h (N=18)	+2.1	<0.0001	+2.6	<0.0001

Figure 2: Rapid and sustained increase in mean functional AAT levels from baseline in all dose groups compared to placebo

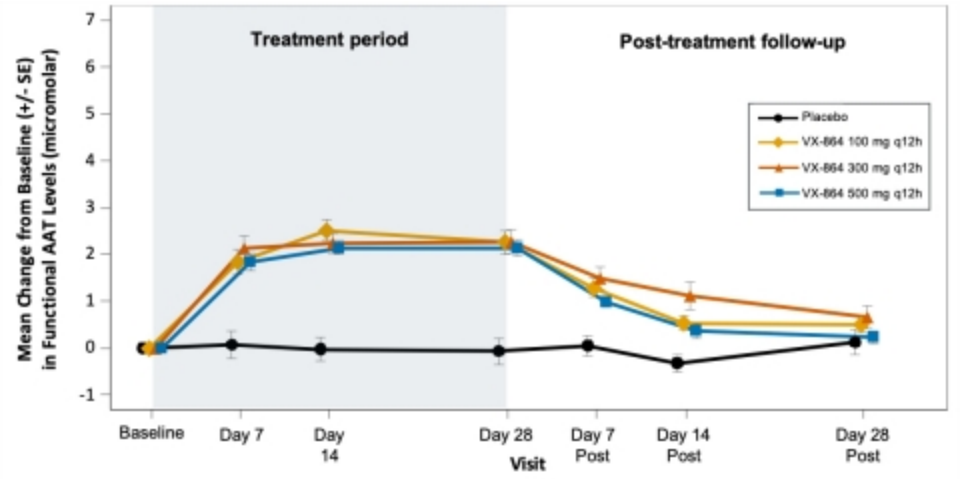

Figure 3: Absolute mean functional and antigenic AAT levels at baseline and at day 28

	Functional AAT (micromolar)		Antigenic AAT (micromolar)	
	Baseline	Day 28	Baseline	Day 28
Placebo (N=7)	4.7	4.6	5.4	5.3
VX-864 100 mg q12h (N=10)	4.0	6.3	4.5	7.9
VX-864 300 mg q12h (N=9)	3.8	6.1	4.6	7.5
VX-864 500 mg q12h (N=18)	4.1	6.2	4.8	7.5

Safety Results

In this study, VX-864 was generally well tolerated. All but one patient completed treatment. There were no discontinuations due to adverse events (AEs) and there were no serious adverse events (SAEs) considered related to study drug. The majority of AEs were mild or moderate in severity and not treatment limiting. The most common AEs in VX-864 treated patients were diarrhea and nausea. Liver function test (LFT) results were similar between the placebo and VX-864 treated groups, and there was no evidence of any impact on LFT results with VX-864.

Next Steps

The results of the VX-864 study demonstrated proof-of-mechanism with a rapid, consistent and clear effect on functional and antigenic AAT levels and a safety profile consistent with no mechanism-related toxicity. The data collected are anticipated to enable optimization of Vertex's small molecule corrector approach in AATD and the rapid progression of a portfolio of new molecules with the potential for greater clinical efficacy into the clinic in 2022. In addition, the learnings from the VX-864 study are expected to enable efficiencies in clinical trial design, enrollment and execution for future assets.

About the Phase 2 Study in People with AATD

The Phase 2 study was a randomized, double-blind, placebo-controlled study of the efficacy and safety of VX-864 in people with the PiZZ genotype. People were randomized to one of three dose groups of VX-864 or placebo for 28 days. In addition, there was a 28-day follow-up period after the last dose of treatment. The primary outcome measures were the mean change from baseline in plasma fAAT levels at day 28 compared to placebo as well as safety and tolerability of VX-864.

About Alpha-1 Antitrypsin Deficiency

AATD is a rare, genetic disease characterized by a protein folding defect which can lead to liver and lung disease. AATD is caused by changes in the *SERPINA1* gene that encodes the AAT protein. In the most common form of AATD, which occurs in people with a PiZZ genotype, these changes to *SERPINA1* cause the body to produce misfolded AAT protein that gets trapped inside the liver, where most AAT is made. This leads to low levels of AAT protein in the blood. Low blood levels of AAT can allow inflammation to proceed unchecked and damage the lungs. The accumulation of defective AAT in the liver can also lead to liver disease. There is currently no cure for AATD. There are also no treatments that target the underlying protein folding defect that is the cause of the disease.

Investor Webcast

The conference call will be webcast live, and a link to the webcast can be accessed on the Vertex website at www.vrtx.com in the "Investors" section. To access the call via phone, please dial (866) 501-1537 (U.S.) 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. An archived webcast will be available on the companies' website for approximately 30 days.

Special Note Regarding Forward-Looking Statements

This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended, including,

without limitation, (i) statements by Dr. Carmen Bozic in this press release, (ii) statements regarding the company's plans to advance additional novel small molecule(s) for AATD into the clinic in 2022 and (iii) the statements set forth under the caption "Next Steps" in this press release. 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 risks and uncertainties that could cause actual events or results to differ materially from those expressed or implied by such forward-looking statements. Those risks and uncertainties include, among other things, risks related to the company's AATD research programs, that data from the company's research and development programs may not support registration or further development of its compounds due to safety, efficacy, or other reasons, and other risks listed under the heading "Risk Factors" in Vertex's most recent annual report filed with the Securities and Exchange Commission at www.sec.gov and available through the company's website at www.vrtx.com. You should not place undue reliance on these statements. Vertex disclaims any obligation to update the information contained in this press release as new information becomes available.

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Vertex Pharmaceuticals Incorporated

Investors:
Michael Partridge, +1 617-341-6108
or
Brenda Eustace, +1 617-341-6187
or
Manisha Pai, +1 617-429-6891

Media:
mediainfo@vrtx.com
or
U.S.: +1 617-341-6992
or
Heather Nichols: +1 617-839-3607
or
International: +44 20 3204 5275

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