October 9, 2014

Vertex Reviews Recent Progress and Announces Upcoming Milestones in the Development of Multiple Combinations of Medicines that Target the Underlying Cause of Cystic Fibrosis

-Data from across Vertex's cystic fibrosis research and development programs to be presented at the 28th Annual North American Cystic Fibrosis Conference (NACFC) beginning today-

-Interim analysis of rollover study following the Phase 3 TRAFFIC and TRANSPORT studies showed sustained improvements in lung function through 48 weeks of treatment with lumacaftor in combination with ivacaftor in people with two copies of the F508del mutation-

-Phase 3 pivotal program of VX-661 in combination with ivacaftor planned for the first half of 2015 in people with 1 or 2 copies of the F508del mutation, pending regulatory discussions and data from a fully enrolled 12-week Phase 2b study of VX-661 and ivacaftor-

-New Drug Application submitted for approval of ivacaftor in children ages 2 to 5 with specific mutations in the CFTR gene-

ATLANTA--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq:VRTX) today reviewed recent progress and announced upcoming milestones in its efforts to develop multiple combinations of medicines that treat the underlying cause of cystic fibrosis (CF) for the majority of people with the disease. These updates were made in conjunction with the 28th Annual North American Cystic Fibrosis Conference (NACFC), which begins today in Atlanta. The company will webcast an investor presentation from the conference at 6:15 p.m. ET on Friday, October 10. The webcast can be accessed live through Vertex's website.

KALYDECO® (ivacaftor) is currently approved to treat more than 2,600 people ages 6 and older in North America, Europe and Australia who have specific mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. In the United States, these mutations include G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P and G1349D. Cystic fibrosis is caused by a defective or missing CFTR protein that results from mutations in the *CFTR* gene. Multiple clinical studies are complete, underway or planned that are designed to evaluate whether ivacaftor, used alone or in combination with other potential CF medicines known as CFTR correctors, may help more people with CF, including people with one or two copies of the most common mutation, F508del. Data from several of these studies will be presented at NACFC, including the results of the Phase 3 TRAFFIC and TRANSPORT studies of the CFTR corrector lumacaftor in combination with ivacaftor, as well as the first interim data from a rollover study of patients who completed treatment in TRAFFIC and TRANSPORT. Other presentations include data from Phase 2 and 3 studies of ivacaftor and Phase 2 studies of VX-661, Vertex's second CFTR corrector, in combination with ivacaftor. Additionally, Vertex today announced that it plans to initiate a pivotal Phase 3 development program for VX-661 in combination with ivacaftor that will evaluate people with CF who have one or two copies of the F508del mutation, including people whose second *CFTR* mutation is known to cause a defect in the gating of the CFTR protein, pending regulatory discussions and data from an ongoing 12-week Phase 2b study of VX-661 in combination with ivacaftor in people with two copies of the F508del mutation.

"With KALYDECO, we have shown that treating the underlying cause of CF can have significant and sustained benefits for people with the G551D mutation," said Jeffrey Chodakewitz, M.D., Senior Vice President and Chief Medical Officer at Vertex. "Our goal is to develop combinations of medicines to treat many more people with CF and to improve the benefit that these combinations of medicines may provide. Data from the Phase 3 studies of lumacaftor in combination with ivacaftor showed consistent evidence of clinical benefit in lung function and other measures of the disease for people with two copies of the F508del mutation and provided important support to conduct further studies of combination regimens aimed at treating people with one and two copies of the F508del mutation."

Lumacaftor in Combination with Ivacaftor

NDA and MAA Planned in the Fourth Quarter: In June 2014, Vertex announced results from the Phase 3 TRAFFIC and TRANSPORT studies of lumacaftor in combination with ivacaftor in people with CF who have two copies of the F508del mutation. Based on the results of these studies, Vertex plans to submit a New Drug Application (NDA) in the United States and

Marketing Authorization Application (MAA) in Europe in the fourth quarter of 2014. The global regulatory submissions will seek approval for the use of lumacaftor (400 mg q12h) in combination with ivacaftor (250 mg q12h) in people ages 12 and older with two copies of the F508del mutation. The combination of lumacaftor and ivacaftor will be fully co-formulated and dosed as two individual tablets every 12 hours (four tablets daily). There are approximately 22,000 people ages 12 and older who have two copies of the F508del mutation in North America, Europe and Australia, including approximately 8,500 in the United States and approximately 12,000 in Europe.

Sustained Improvements in Lung Function Through 48 Weeks of Treatment: Patients who completed 24 weeks of treatment in either TRAFFIC or TRANSPORT were able to enter a Phase 3 rollover study to receive a combination regimen. One thousand thirty-one people started treatment in the rollover study, and at the time of the interim analysis, approximately 25 percent of patients within each arm of the rollover study had received an additional 24 weeks of treatment for a total of 48 weeks of treatment (48 weeks of treatment with a combination regimen for patients who received a combination regimen in TRAFFIC and TRANSPORT; 24 weeks of treatment with a combination regimen for patients who received placebo in TRAFFIC and TRANSPORT).

The first interim data from this rollover study will be presented at NACFC and showed that the initial improvements in lung function (percent predicted forced expiratory volume in one second, or ppFEV1) observed in the 24-week TRAFFIC and TRANSPORT studies were sustained through 48 weeks of treatment with lumacaftor in combination with ivacaftor. The pattern of response observed after the initiation of combination dosing across all patients who received placebo in TRAFFIC and TRANSPORT and subsequently received a combination regimen in the rollover study was similar to that seen in patients who received a combination regimen in TRAFFIC and TRANSPORT.

At the time of the interim analysis, the safety and tolerability results, including the rate of serious adverse events, were consistent with those observed in the Phase 3 TRAFFIC and TRANSPORT studies. Among patients new to treatment in the rollover study, infective pulmonary exacerbation, cough, increased sputum, haemoptysis, respiration abnormal and dyspnea were the most common adverse events at the time of the interim analysis.

Results from TRAFFIC and TRANSPORT and from the interim analysis of the rollover study will be presented as part of an oral invited talk at NACFC ("Effect of lumacaftor in combination with ivacaftor in patients with cystic fibrosis who are homozygous for F508del-CFTR: Phase 3 TRAFFIC & TRANSPORT studies." Symposium Session II on October 10 at 11:30 a.m. ET. Posters 249 and 250).

VX-661 in Combination with Ivacaftor

VX-661 is Vertex's second CFTR corrector and is being developed to play a role in multiple combinations of CFTR modulators aimed at treating people with CF who have one or two copies of the F508del mutation.

Enrollment Complete in 12-week Phase 2 Study: VX-661 is currently being evaluated in combination with ivacaftor as part of a 12-week Phase 2b study in people ages 18 and older who have two copies of the F508del mutation. Vertex today announced that this study is fully enrolled and that data will be available in early 2015.

Pivotal Phase 3 Program of VX-661 Planned for First Half of 2015: Vertex today announced plans to initiate a pivotal Phase 3 clinical program of VX-661 in combination with ivacaftor in the first half of 2015, pending regulatory discussions and data from the ongoing 12-week Phase 2b study in people with two copies of the F508del mutation. This Phase 3 program is expected to evaluate efficacy and safety of VX-661 in combination with ivacaftor in people with the following *CFTR* mutations:

- **Two Copies of the F508del Mutation**, based on previously announced data from a Phase 2 study of VX-661 in combination with ivacaftor in people with two copies of the F508del mutation to be presented at NACFC ("Phase 2 studies reveal additive effects of VX-661, an investigational CFTR corrector, and ivacaftor, a CFTR potentiator, in patients with CF who carry the F508del-CFTR mutation." An oral presentation of these data will be delivered as part of an invited talk during Symposium Session II on October 10 at 11:55 a.m. ET).
- **One Copy of the F508del Mutation and a Second Mutation That Results in a Gating Defect in the CFTR Protein**, based on data announced in mid-2014 from a Phase 2 proof-of-concept study in people with the F508del mutation and G551D mutation to be presented at NACFC ("Addition of VX-661, an investigational CFTR corrector, to ivacaftor, a CFTR potentiator, in patients with CF and heterozygous for F508del/G551D-CFTR." Poster 260).
- **One Copy of the F508del Mutation and a Second Mutation That Results in Residual CFTR Function**, based on data announced in mid-2014 from a Phase 2 proof-of-concept study of ivacaftor in people with a residual function mutation to be presented at NACFC ("Effect of ivacaftor in patients with cystic fibrosis, residual CFTR function and FEV_1 ≥ 40% of predicted, N-of-1 study." Poster 196. An oral presentation of these data will also be delivered during Workshop Session III on October 11 at 3:00 p.m. ET). Additionally, based on data from the Phase 2 study of ivacaftor in people with a residual function mutation, referenced above, Vertex plans to evaluate ivacaftor used as monotherapy in people with these mutations as part of the pivotal program.

- **One Copy of the F508del Mutation and A Second Mutation That Results in Minimal CFTR Function -** The evaluation of people with one copy of the F508del mutation and one copy of a *CFTR* mutation that results in minimal CFTR function as part of the pivotal Phase 3 program would be the first evaluation of VX-661 in combination with ivacaftor in people with these mutations. To date, treatment with a combination of lumacaftor and ivacaftor has not resulted in a significant improvement in lung function for people with these mutations.

Planning for the pivotal Phase 3 program is underway to support the initiation of enrollment in the first half of 2015, pending regulatory discussions planned for later this year and the data from the ongoing Phase 2b study, which are expected in early 2015.

Triple Combination of VX-661, Ivacaftor and a Next-Generation Corrector: Vertex has multiple next-generation correctors in the lead-optimization stage of research and expects to begin clinical development of a next-generation corrector in 2015. *In vitro* data showed that a triple combination of VX-661, ivacaftor and a next-generation corrector resulted in increased chloride transport in human bronchial epithelial cells with one or two copies of the F508del mutation, as compared to the use of a single corrector in combination with ivacaftor.

KALYDECO (ivacaftor)

Study of Ivacaftor in People with the R117H Mutation: Data from a Phase 3 study of ivacaftor in people ages 6 and older who have the R117H mutation will be presented at NACFC ("Effects of ivacaftor in CF patients with R117H-CFTR." Poster 17. An oral presentation of these data will also be delivered during Workshop Session II on October 10 at 3:25 p.m. ET). As previously announced, the Phase 3 study did not meet its primary endpoint of the absolute change from baseline in percent predicted forced expiratory volume in one second (ppFEV1) through 24 weeks of treatment, however a pre-specified subset analysis in patients ages 18 and older showed statistically significant improvements in lung function and other key secondary endpoints. The safety and tolerability results observed in this study were consistent with those observed in prior Phase 3 studies of ivacaftor monotherapy in people with CF who have the G551D or other gating mutations.

Based on the Phase 3 data, Vertex submitted an sNDA in the U.S. and MAA variation in Europe for approval of ivacaftor in people with the R117H mutation. Vertex's sNDA for the use of ivacaftor in people with the R117H mutation will be the subject of an FDA Advisory Committee Meeting of the Pulmonary-Allergy Drugs Division on October 21, 2014. In the United States, Vertex is seeking approval of ivacaftor in people ages 6 and older with the R117H mutation.

NDA and MAA Line Extension Submissions for Use of Ivacaftor in Children Ages 2 to 5: Vertex today announced the submission of an NDA in the United States for the approval of ivacaftor in children with CF ages 2 to 5 who have one of the following nine mutations in the *CFTR* gene: G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P or G1349D. Vertex expects to complete the MAA line extension application in Europe this week. In the United States and Europe, KALYDECO is currently approved for use in people with CF ages 6 and older who have one of these nine mutations.

The submissions were based on results announced today and being presented at NACFC from an open-label Phase 3 study that was designed to evaluate the pharmacokinetics and safety of weight-based dosing of ivacaftor to support approval in children ages 2 to 5 ("An open-label study of the safety, pharmacokinetics & pharmacodynamics of ivacaftor in patients aged 2 to 5 years with CF & a CFTR Gating Mutation: The KIWI Study." Poster 200. An oral presentation of these data will also be delivered during Workshop Session III on October 11 at 4:00 p.m. ET). The first part of the study evaluated pharmacokinetics and safety of ivacaftor treatment over four days to support the evaluation of ivacaftor for 24 weeks in the second part of the study. The primary endpoint of the second part of the study was safety.

In the second part of the study (n=34), ivacaftor was generally well tolerated and the majority of adverse events were mild or moderate in severity. Five patients who had elevated liver enzymes at baseline (greater than two times the upper limit of normal) experienced further elevations of liver enzymes to greater than eight times the upper limit of normal during the study. One patient experienced a serious adverse event related to elevated liver enzymes, and this patient discontinued treatment from the study. For all five patients, liver enzymes returned to their baseline levels following interruption of ivacaftor. Serious adverse events occurred in 18 percent (6 of 34) of patients, and the most common adverse events, regardless of dose group, were cough, vomiting, nasal congestion, upper respiratory tract infection and rhinorrhea.

In addition, secondary endpoints showed decreases in sweat chloride and improvements in nutritional status as measured by change in weight (weight-for-age z score) and body mass index (BMI-for-age z score).

Based on results from this study, Vertex is seeking approval of a 50 mg and 75 mg weight-based dose of ivacaftor for children ages 2 to 5. For children in this age group, a granule (mini-tablet) formulation will be used to enable administration of ivacaftor in soft foods as opposed to the current tablet formulation for people 6 years and older.

INDICATION AND IMPORTANT SAFETY INFORMATION FOR KALYDECO® (ivacaftor)

Ivacaftor (150 mg tablets) is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a *G551D* mutation in the *CFTR* gene.

In the United States and the European Union, ivacaftor is also indicated for the treatment of CF in patients age 6 and older who have one of the following mutations in the *CFTR* gene: *G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R*. In Canada, ivacaftor is indicated for these same mutations and additionally for *G970R*.

Ivacaftor is not effective in patients with CF with 2 copies of the *F508del* mutation (*F508del/F508del*) in the *CFTR* gene. The safety and efficacy of ivacaftor in children with CF younger than 6 years of age have not been established.

Elevated liver enzymes (transaminases; ALT and AST) have been reported in patients receiving ivacaftor. It is recommended that ALT and AST be assessed prior to initiating ivacaftor, every 3 months during the first year of treatment, and annually thereafter. Patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the upper limit of normal. Following resolution of transaminase elevations, consider the benefits and risks of resuming ivacaftor dosing.

Use of ivacaftor with medicines that are strong CYP3A inducers, such as the antibiotics rifampin and rifabutin; seizure medications (phenobarbital, carbamazepine, or phenytoin); and the herbal supplement St. John's Wort, substantially decreases exposure of ivacaftor and may diminish effectiveness. Therefore, co-administration is not recommended.

The dose of ivacaftor must be adjusted when used concomitantly with strong and moderate CYP3A inhibitors or when used in patients with moderate or severe hepatic disease.

Ivacaftor can cause serious adverse reactions including abdominal pain and high liver enzymes in the blood. The most common side effects associated with ivacaftor include headache; upper respiratory tract infection (the common cold), including sore throat, nasal or sinus congestion, and runny nose; stomach (abdominal) pain; diarrhea; rash; and dizziness. These are not all the possible side effects of ivacaftor. A list of the adverse reactions can be found in the product labeling for each country where ivacaftor is approved. Patients should tell their healthcare providers about any side effect that bothers them or does not go away.

Please see KALYDECO U.S. Prescribing Information, EU Summary of Product Characteristics, Canadian Product Monograph, Australian Consumer Medicine Information and Product Information, Swiss Prescribing Information and Patient Information, and the New Zealand Datasheet and Consumer Medicine Information.

About Cystic Fibrosis

Cystic fibrosis is a rare, life-threatening genetic disease affecting approximately 75,000 people in North America, Europe and Australia. Today, the median predicted age of survival for a person with CF is between 34 and 47 years, but the median 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 1,900 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 protein at the cell surface. The defective function or absence of CFTR proteins in people with CF results in poor flow of salt and water into and out of the cell in a number of organs, including the lungs. This leads to the buildup of abnormally thick, sticky mucus that can cause chronic lung infections and progressive lung damage.

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 nonprofit drug discovery and development affiliate of the Cystic Fibrosis Foundation. This collaboration was expanded to support the accelerated discovery and development of Vertex's CFTR modulators.

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 four 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.

Investor Event Webcast

The company will host an investor event at 6:15 p.m. ET on Friday, October 10 at NACF. To listen to management's live presentation from the event, please dial (866) 501-1537 (U.S.) or +1 (720) 545-0001 (International). The event will also be webcast and a link to the live webcast can be accessed through Vertex's website at www.vrtx.com in the "Investors" section under the "Events and Presentations" link. Conference call and webcast participants will be in a listen-only mode. An archived webcast of the presentation will be available on the company's website.

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 of the press release, and the information provided regarding (i) the planned Phase 3 pivotal program of VX-661 in combination with ivacaftor; (ii) planned and ongoing studies of ivacaftor, used alone or in combination with CFTR correctors; (iii) the data that is expected to be presented at NACFC; (iv) plans to submit regulatory applications, including plans to submit an NDA and MAA for lumacaftor in combination with ivacaftor in the fourth quarter of 2014; and (v) Vertex's next-generation corrector research program. 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, that data from the company's development programs may not support registration or further development of its compounds, that Vertex could experience unforeseen delays in submitting regulatory filings, that regulatory authorities may not approve, or approve on a timely basis, lumacaftor in combination with ivacaftor or ivacaftor for additional indications 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.

(VRTX-GEN)

Vertex Pharmaceuticals Incorporated
Investors:
Michael Partridge, 617-341-6108
or
Kelly Lewis, 617-961-7530
or
Media:
North America: Zach Barber, 617-341-6470
or
Europe and Australia: Megan Goulart, +41 22 593 6066
mediainfo@vrtx.com

Source: Vertex Pharmaceuticals Incorporated

News Provided by Acquire Media