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AASLD Presentations Support the Initiation of a Broad Phase II Program with VX-950, an Investigational Oral HCV Protease Inhibitor

Vertex Announces Filing of IND in Support of VX-950 Phase II Development in the U.S.

San Francisco, CA, November 11, 2005 - Clinical data being presented this week while attending the 56th American Association for the Study of Liver Diseases (AASLD) Annual Meeting confirm that VX-950, an investigational oral hepatitis C protease inhibitor developed by Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX), was well-tolerated and possessed potent antiviral activity in a 14-day study in patients with hepatitis C virus (HCV) infection. The rapid decline in plasma HCV-RNA levels observed in HCV patients taking VX-950, together with a viral kinetic analysis that projects the potential duration of treatment required to achieve sustained virologic response (SVR), support the evaluation of VX-950 in a novel, three-month combination treatment paradigm. Vertex also announced today that it has filed an investigational new drug application (IND) with the U.S. Food and Drug Administration (FDA) to support Phase II clinical development of VX-950.

"The clinical data demonstrate a swift and dramatic decline in viral levels with VX-950, and provide insight into VX-950's potential to transform future HCV treatment," said Joshua Boger, Ph.D., Chairman, President and Chief Executive Officer of Vertex. "Our clinical development effort is gaining momentum, as indicated by our recent IND submission with the FDA to support the planned initiation before year-end of the first clinical study in what we expect will be a broad Phase II program."

Phase Ib Study Clinical Results: Major Findings

Five presentations taking place at the meeting provide a comprehensive analysis of the Phase Ib study of VX-950 given as monotherapy. Results being presented at the conference are from a dose-ranging Phase Ib study of VX-950 dosed in an oral suspension for 14 days in patients with chronic hepatitis C. Dr. Henk Reesink, Principal Investigator for the study, will present the major findings in an oral presentation at the Presidential Plenary Session and at a press conference on Monday, November 14. In the Phase Ib study, VX-950 in all dose groups exhibited substantial antiviral effects, with 26 of 28 patients receiving any dose of VX-950 achieving more than a 3-log reduction in plasma HCV-RNA within two days. After 14 days, patients in the best dose group (750 mg every 8 hours) achieved a mean reduction in HCV-RNA of 4.4 log10, a 25,000-fold reduction in viral levels. In the trial, VX-950 was well-tolerated. Overall in the Phase Ib study, adverse events observed in patients receiving VX-950 that were considered possibly related to the drug were mild, and generally similar in frequency to events in the placebo group. The most common adverse events reported in both placebo and VX-950 patients were headache, frequent urination, and gastrointestinal symptoms.1

In a separate analysis of the Phase Ib trial results to be presented in detail in a poster presentation on Tuesday, November 15, Vertex researchers analyzed the relationship between blood concentrations of VX-950 and antiviral effect over 14 days. A dose-response was established with higher ranges of VX-950 blood concentrations being associated with a better outcome relative to the responses established at lower blood concentrations of VX-950. The researchers found that the steep decline in plasma HCV-RNA seen in patients during the first two days was correlated closely with total blood concentrations during the first dosing interval, as measured by area under the curve (AUC). In addition, the achievement of a greater than 3.5 log10 reduction in plasma HCV-RNA at day 7 or greater than 4.5 log10 reduction at the end of the full 14 days of treatment was closely correlated with blood concentrations at "trough" (minimum concentration in blood immediately prior to receiving the next dose).

Further, these researchers analyzed the viral kinetics to estimate the treatment duration required to achieve viral eradication. In this analysis, researchers projected the continued slope of viral decline that could be expected with dosing beyond 14 days in the patients who achieved HCV-RNA levels below the limit of quantitation at the end of dosing in the Phase Ib study. The results of this simulation suggest that, with continued steep viral decline on treatment, it may be possible with approximately 12 weeks of treatment to reduce levels of HCV-RNA in patients to less than 10 viral copies (total body viral load). A total body viral load in this range is considered to be what may be required for potential host eradication of infection and achievement of SVR. Vertex is taking the encouraging results of this viral kinetic analysis into account in the design of planned Phase II clinical studies of up to 12 weeks duration.2

"The complete data set for the Phase Ib study suggests that VX-950 is well-tolerated and can substantially reduce virus in a 14-day study," said Henk W. Reesink, MD, Associate Professor of Medicine at Academic Medical Center in Amsterdam. "The results of the blood-concentration versus antiviral effect analysis are encouraging because they indicate that optimal antiviral

response could be maintained if certain trough concentrations are achieved. Moreover, the viral kinetic analysis supports the evaluation of VX-950, at doses that maintain the target trough concentration, in a novel treatment paradigm of 12 weeks duration."

Phase Ib Study: Viral Sequencing Results

In a further analysis planned for presentation on Monday, November 14, researchers used a novel sequencing approach to analyze the sequences of the HCV NS3 protease gene in samples isolated from patients prior to and following treatment in the Phase Ib study from all dose groups, including suboptimal dose groups. The relative frequencies of wild-type and variant virus, as well as the sensitivity of variant protease enzymes to inhibition by VX-950 in vitro, were assessed and correlated with the viral load response obtained during dosing with VX-950. Three categories of HCV-RNA response were identified: continued decline (decline in HCV-RNA from day 1 through day 14), viral rebound (increase in HCV-RNA between nadir and day 14), and plateau response (minimal change in HCV-RNA between nadir and day 14). The patients with a continued decline in HCV-RNA had the highest mean trough VX-950 concentration, while the patients with viral rebound had the lowest mean trough blood concentrations.

In the group of patients with continued viral decline on treatment, HCV-RNA levels at the end-of-dosing were below the limit of detection (less than 100 IU/mL) of the sequencing assay. At 7-10 days post-treatment, virus could again be isolated. In the post-treatment period, wild-type virus predominated, with some variants detected that displayed a minimally-reduced sensitivity to VX-950 in vitro. In the other two groups of patients, sequence changes associated with reduced sensitivity to VX-950 in vitro were detected at the end-of-dosing, including some variants with moderately- to highly-reduced sensitivity to VX-950. However, these sequence changes also appeared to result in reduced viral fitness. In particular, the frequency of the variant (A156V/T) with the highest level of reduced drug sensitivity diminished markedly between the end-of-dosing and post-treatment analysis, indicating significantly reduced in vivo fitness relative to wild-type virus. Published in vitro data indicate that the A156V/T variant also retains sensitivity to interferon.3

"This is the first study that has attempted to comprehensively characterize HCV protease variants that may emerge during treatment with a potent direct-acting antiviral compound. As expected, selection of certain variants was associated with suboptimal drug levels and a suboptimal initial decline of HCV-RNA concentrations that led to either viral rebound or a plateau in viral response," said Christoph Sarrazin, MD, Saarland University Hospital, Homburg, Germany, and Study Investigator. "It is encouraging that patients with the highest blood concentrations of VX-950 achieved continuous decline in viral load levels over the entire dosing period, suggesting that achieving sufficient trough concentrations could suppress the viral variants associated with viral rebound. Further, the sequencing results provide a strong rationale for the combination of VX-950 and pegylated interferon to achieve optimal response rates."

Additional Data Presentations

Two additional abstracts related to VX-950 will be presented at the conference. In one abstract, researchers showed that despite heterogeneity among viral sequences that could be isolated from patients prior to treatment, all isolates were sensitive to VX-950 in vitro. Minor viral variants that may have existed at a frequency of less than 2 percent would not have been detected with the approach utilized.4 In another abstract, researchers found that patients receiving VX-950 in the Phase Ib study rapidly achieved substantial reductions in alanine aminotransferase (ALT) levels after 14 days of treatment. In addition, changes in median neopterin levels correlated with decreases in HCV-RNA and ALT during administration of VX-950, suggesting that inhibition of HCV replication by VX-950 may decrease inflammation and tissue damage.5

Clinical and Regulatory Milestones

Vertex recently announced the initiation of a 14-day Phase Ib combination study of VX-950 and pegylated interferon in Europe, using a new tablet formulation that is expected to achieve significantly higher blood concentrations compared to the oral suspension formulation used previously. Today, Vertex announced the filing of an IND to support Phase II clinical development of VX-950. Vertex also affirmed today that it remains on track to initiate by year-end a 28-day, Phase II combination study of VX-950 and pegylated interferon.

About Hepatitis C

Hepatitis C is a liver disease caused by the hepatitis C virus, which is found in the blood of people with the disease. HCV, a serious public health concern affecting 3.4 million individuals in the United States, is spread through direct contact with the blood of infected people. Though many people with hepatitis C may not experience symptoms, others may have symptoms such as jaundice, abdominal pain, fatigue and fever. Hepatitis C significantly increases a person's risk for developing long-term infection or chronic liver disease. It also increases a person's risk of developing cirrhosis and of dying from a long-term infection.

About VX-950

VX-950 is an oral inhibitor of hepatitis C virus protease, an enzyme essential for viral replication. Vertex researchers were the first to solve the three-dimensional crystal structure of HCV protease, and have used structural insights to enable the design of small molecule HCV protease inhibitors, including VX-950.

The VX04-950-101 clinical study being reported at AASLD was a dose-range finding study that included three panels of eight healthy subjects each (Part A) and three panels of 12 patients with genotype-1 HCV (Part B). In Part A, subjects were dosed for five days at doses of 450 mg, 750 mg or 1250 mg every eight hours, or placebo. Data from Part A were reported in May 2005 at the Digestive Disease Week meeting. In Part B, patients were dosed for 14 days at doses of 450 mg or 750 mg every eight hours, or 1250 mg every 12 hours or placebo. The objectives of the study were to assess safety, tolerability and antiviral activity in patients with HCV.

About Vertex

Vertex Pharmaceuticals Incorporated is a global biotechnology company committed to the discovery and development of breakthrough small molecule drugs for serious diseases. The Company's strategy is to commercialize its products both independently and in collaboration with major pharmaceutical companies. Vertex's product pipeline is principally focused on viral diseases, inflammation, autoimmune diseases and cancer. Vertex co-promotes the HIV protease inhibitor, Lexiva, with GlaxoSmithKline.

Lexiva is a registered trademark of the GlaxoSmithKline group of companies.

Conference Call on November 11, 2005
Vertex Pharmaceuticals will host a conference call on November 11, 2005 at 9:00 a.m. ET to review clinical results and recent developments. This call will be broadcast via the Internet at www.vrtx.com in the investor center. Alternatively, to listen to the call on the telephone, dial (800) 374-0296 (U.S. and Canada) or (706) 634-2224 (International).

The call will be available for replay via telephone commencing November 11, 2005 at 11:00 a.m. ET running through 5:00 p.m. ET on November 18, 2005. The replay phone number for the U.S. and Canada is (800) 642-1687. The international replay number is (706) 645-9291 and the conference ID number is 2361425. Following the live webcast, an archived version will be available on Vertex's website until 5:00 p.m. ET on November 25, 2005.

Safe Harbor Statement

This press release may contain forward-looking statements, including statements that (i) VX-950 could be part of a novel treatment paradigm with the potential to transform future HCV treatment; (ii) Vertex plans to initiate a Phase II study before year-end, as the first of what could be a broad Phase II program; (iii) simulations of the projected slope of viral decline suggest a potential treatment regimen of approximately 12 weeks; and (iv) study data suggests that VX-950 is well-tolerated, that achieving sufficient trough blood-level concentrations could suppress the viral variants associated with viral rebound and that inhibition of HCV replication by VX-950 may decrease inflammation and tissue damage. While management makes its best efforts to be accurate in making forward-looking statements, such statements are subject to risks and uncertainties that could cause Vertex's actual results to vary materially. These risks and uncertainties include, among other things, the risks that clinical trials for VX-950 may not proceed as planned due to technical, scientific, or patient enrollment issues, or disagreements with regulatory authorities over trial design or other matters, that the scale and scope of future clinical and nonclinical studies may change and will be determined in significant part by data collected in ongoing and future trials, that further clinical studies of VX-950 may not reflect the results obtained in the early clinical and nonclinical studies which are the subject of this release, and other risks listed under Risk Factors in Vertex's form 10-K filed with the Securities and Exchange Commission on March 16, 2005.

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1Reesink et al, "Final results of a Phase Ib, Multiple-dose study of VX-950, a hepatitis C virus protease inhibitor," American Association for the Study of Liver Diseases, 56th Annual Meeting, Presentation #95, November 11-15, 2005.

2Chu et al, "Pharmacokinetics of VX-950, and its effect on hepatitis C viral dynamics," American Association for the Study of Liver Diseases, 56th Annual Meeting, Presentation #1260, November 11-15, 2005.

3C. Lin et al, "In vitro studies of cross-resistance mutations against two hepatitis C virus serine protease inhibitors, VX-950 and BILN 2061," Journal of Biological Chemistry, 208:44, November 2005.

4Kieffer et al, "Genetic heterogeneity in the HCV NS3 protease of untreated genotype 1 patients has little effect on the

sensitivity to VX-950," American Association for the Study of Liver Diseases, 56th Annual Meeting, Presentation #867, November 11-15, 2005.

5Gelderblom et al, "Decline in serum neopterin concentration correlates with HCV-RNA decline during administration of VX-950, a hepatitis C virus protease inhibitor," American Association for the Study of Liver Diseases, 56th Annual Meeting, Presentation #859, November 11-15, 2005.