**4-Drug Combo with Telaprevir and VX-222 Clears
HCV at 12 Weeks**

**EASL**

4/5/11

[Telaprevir](http://www.hivandhepatitis.com/hep_c/hepc_news_alter.html#vx) is Vertex's lead investigational hepatitis C virus (HCV) protease inhibitor, which is currently undergoing review by the U.S. Food and Drug Administration (FDA). VX-222 is a non-nucleoside HCV polymerase inhibitor.

Investigators presented 12-week results from the Phase 2 ZENITH trial at the European Association for the Study of the Liver's International Liver Congress ([EASL 2011](http://www.hivandhepatitis.com/2011_conference/easl2011/main.html)) this week in Berlin.

The study initially compared telaprevir plus VX-222 alone vs these 2 drugs with standard therapy using [pegylated interferon alfa-2a (Pegasys) plus ribavirin](http://www.hivandhepatitis.com/hep_c/hepc_news_comb.html). The all-oral 2-drug arms were halted early due to viral breakthrough. The trial continued testing the 4-drug combo, and researchers also added a 3-drug interferon-sparing regimen consisting of telaprevir, VX-222, and ribavirin.

*Below is an edited excerpt from a press release issued by Vertex describing the ZENITH study and its preliminary findings.*

**Interim Phase 2 Data Showed Rapid Viral Response to VX-222
in Combination with Telaprevir, Pegylated Interferon
and Ribavirin Among People With Hepatitis C**

*First study to evaluate four-drug, 12-week treatment duration for hepatitis C*

Berlin -- March 31, 2011 -- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced interim results from an ongoing Phase 2 study (ZENITH) designed to assess the safety and tolerability of 12-week response-guided treatment regimens with its polymerase inhibitor, VX-222, and its protease inhibitor, telaprevir, in combination with pegylated interferon and ribavirin in people with genotype 1 chronic hepatitis C who were new to treatment.

The study enrolled 106 people into one of four treatment groups. Among those who received VX-222 (400 mg) in combination with telaprevir, pegylated-interferon and ribavirin, interim data showed that 90 percent (27/30) of them had undetectable hepatitis C virus at week 12. Half (15/30) of those in the VX-222 (400 mg) treatment group were eligible to stop all treatment at week 12. People in this same treatment group who were not eligible to stop all treatment at 12 weeks were assigned to receive 24 total weeks of treatment: 12 weeks of the four-drug regimen followed by 12 weeks of pegylated-interferon and ribavirin alone.

Preliminary safety results showed that the most frequently reported adverse events were mild gastrointestinal symptoms and mild fatigue. At the time of this analysis, there were no discontinuations due to gastrointestinal symptoms. Data from this study are being presented today at The International Liver Congress 2011, the 46th annual meeting of the European Association for the Study of the Liver (EASL) in Berlin, Germany.

"Telaprevir triple therapy demonstrated significant improvements in viral cure rates and an ability to halve treatment time to 24 weeks for many people in late-stage studies," said Robert Kauffman, MD, PhD, Senior Vice President and Chief Medical Officer for Vertex. "Reducing treatment time in half again to 12 weeks would be another important advance and the early data from this study provide new information about the potential to do this with a four-drug VX-222 regimen."

Using an intent-to-treat analysis, 57 percent (17/30) of people treated with VX-222 (400 mg) in combination with telaprevir, pegylated interferon and ribavirin had undetectable hepatitis C virus by week two. Among people who were treated with VX-222 (100 mg) in combination with telaprevir, pegylated interferon and ribavirin, 38 percent (11/29) had undetectable hepatitis C virus by week two.

To determine if patients were eligible to stop all treatment at 12 weeks in ZENITH, they had to have undetectable hepatitis C virus at weeks two and eight. Using the eligibility criteria for a 12-week total treatment duration, half (15/30) of the patients in the high-dose VX-222 combination group and 38 percent (11/29) in the low-dose combination group were eligible to stop all treatment at 12 weeks. Ninety percent (27/30) of patients in the high-dose VX-222 group had undetectable hepatitis C virus by week 12 as did 83 percent (24/29) in the low-dose VX-222 group. No viral breakthrough was observed through week 12 among patients receiving the four-drug combinations.

"The early data from this study are encouraging because they showed patients had a very rapid decline in hepatitis C virus as early as the second week of treatment," said Adrian Di Bisceglie, MD, Chief of Hepatology at Saint Louis University School of Medicine. "Hepatitis C virus was undetectable at week 12 of treatment in 90 percent of patients who received the higher dose of VX-222, and half of those in this treatment group were eligible to stop all treatment at that time."

ZENITH is an ongoing Phase 2 study that enrolled 106 people and began with four treatment arms evaluating two-drug and four-drug combination regimens. The primary endpoint is safety and tolerability and the secondary endpoint is on-treatment antiviral activity and the proportion of people in each treatment arm who achieve a sustained viral response (SVR, defined as undetectable hepatitis C virus 24 weeks after the end of treatment). The study is designed to evaluate various combinations of VX-222, telaprevir, pegylated-interferon and ribavirin for the treatment of genotype 1 chronic hepatitis C.

In this study, VX-222, telaprevir and ribavirin are given twice daily. Arms A (n=18) and B (n=29) were designed to evaluate the all-oral, two-drug combination regimens of VX-222 (400 mg or 100 mg) and telaprevir (1,125 mg). Both of these study arms were discontinued due to a pre-defined stopping rule related to viral breakthrough. Arms C (n=29) and D (n=30) are ongoing and designed to evaluate the four-drug combination regimens of VX-222 (400 mg and 100 mg), telaprevir (1,125 mg), pegylated-interferon and ribavirin.

An additional treatment arm has been added to the study to evaluate an all-oral, three-drug regimen of VX-222, telaprevir and ribavirin in people with genotype 1b chronic hepatitis C. This study arm is now open for enrollment. A sixth and final arm may be added to the trial per protocol based on data from the study.

|  |
| --- |
| **ZENITH: Interim Intent to Treat (ITT) Analysis of Arms C and D**  |
|  | VX-222 (100 mg) /TVR- based arm(+)  | VX-222 (400 mg) /TVR-based arm(++)  |
| Week 2 HCV RNA undetectable  | 38% (11/29)  | 57% (17/30)  |
| Week 2 and 8 HCV RNA undetectable\*  | 38% (11/29)  | 50% (15/30)  |
| Week 4 HCV RNA undetectable (RVR)  | 86% (25/29)  | 87% (26/30)  |
| Weeks 12 HCV RNA undetectable (eRVR)  | 83% (24/29)  | 90% (27/30)  |
| [TVR = telaprevir; BID = twice-daily]HCV RNA was evaluated using the TaqMan assay version 2.0.  |
| \*As part of a response-guided regimen, people who have undetectable hepatitis C virus at weeks 2 and 8 are eligible to stop all treatment at week 12. +VX-222 (100 mg, BID), telaprevir (1,125 mg, BID), Pegasys (pegylated interferon alfa-2a) and Copegus (ribavirin). ++VX-222 (400 mg, BID), telaprevir (1,125 mg, BID), Pegasys (pegylated-interferon alfa-2a) and Copegus (ribavirin). |

**Preliminary Safety and Tolerability**

The 12-week safety and tolerability results are preliminary and include data on all patients enrolled in the study: those enrolled in the two-drug (n=47) and four-drug (n=59) treatment arms. The most frequent adverse events observed in this study were mild gastrointestinal symptoms (including diarrhea, nausea and vomiting) and mild fatigue. No patients discontinued due to gastrointestinal symptoms.
Preliminary safety data indicate that there were six discontinuations due to adverse events among the four treatment arms through week 12. There were two serious adverse events considered by the investigator to be potentially related to study medication: acute renal failure (Arm B), which resolved after study medications were discontinued and anemia (Arm C). There was one additional severe adverse event reported of pneumonia, septic shock and renal failure; this severe adverse event was considered by the investigator to be unrelated to study medication. The three additional discontinuations included rash (n=2) and a motor vehicle accident with facial fractures (n=1).

**About Telaprevir and VX-222**

Vertex has two oral medicines in development for the treatment of genotype 1 chronic hepatitis C: telaprevir and VX-222. Telaprevir is an investigational, oral inhibitor that acts directly on the HCV protease, an enzyme essential for viral replication. To date, more than 2,500 people with genotype 1 chronic hepatitis C have received telaprevir in Phase 2 and Phase 3 studies. Vertex has been granted Priority Review for its applications for the approval of telaprevir by the U.S. Food and Drug Administration (FDA) and Health Canada. The FDA has scheduled its Antiviral Drugs Advisory Committee to discuss the New Drug Application for telaprevir on April 28, 2011. A target response date of May 23, 2011 is set under the Prescription Drug User Fee Act (PDUFA).

Vertex is developing telaprevir in collaboration with Tibotec BVBA and Mitsubishi Tanabe Pharma. Vertex has rights to commercialize telaprevir in North America. Through its affiliate, Janssen, Tibotec has rights to commercialize telaprevir in Europe, South America, Australia, the Middle East and certain other countries. Mitsubishi Tanabe Pharma has rights to commercialize telaprevir in Japan and certain Far East countries.

VX-222 is an investigational, oral, non-nucleoside inhibitor of HCV NS5B polymerase. VX-222 is currently being evaluated in combination with telaprevir, pegylated-interferon and ribavirin in a Phase 2 study. Vertex has worldwide commercial rights for VX-222.

Vertex Pharmaceuticals. Interim Phase 2 Data Showed Rapid Viral Response to VX-222 in Combination with Telaprevir, Pegylated-Interferon and Ribavirin Among People With Hepatitis C. Press release. March 31, 2011