

## Novel Protease and Polymerase Inhibiting Agents to Treat Chronic Hepatitis C Infection

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A Review of Selected Presentations  
From the 58th Annual Meeting of the American  
Association for the Study of Liver Diseases  
November 2–6, 2007  
Boston, Massachusetts

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A CME Activity  
Approved for  
1.0 AMA PRA  
Category 1 Credit(s)™

**Release date:** February 2008

**Expiration date:** February 28, 2009

**Estimated time to complete activity:** 1.0 hours

Supported through an educational grant  
from Vertex Pharmaceuticals.



Sponsored by Postgraduate Institute for Medicine.

**Target Audience:** This activity has been designed to meet the educational needs of gastroenterologists involved in the management of patients with chronic hepatitis C.

**Statement of Need/Program Overview:** Approximately 3.9 million Americans are currently infected with the hepatitis C virus (HCV), and an estimated 8,000–10,000 deaths each year result from HCV-associated chronic liver disease. Although public health measures instituted over the past two decades have resulted in changes in transmission rates, the major mode of HCV infection continues to be through injection drug use. Other modes of transmission account for a very low percentage of overall infections and include exposure through chronic hemodialysis treatment, accidental exposures in healthcare workers or between household contacts, and sexual activity with an infected partner. HCV infection affects persons of all ages, but most acute cases of hepatitis C and the highest seroprevalence of HCV infection are found among young adults, and the highest incidence and prevalence rates are among nonwhite racial/ethnic groups. Although the incidence of acute hepatitis C has declined in response to public health measures, there is a large reservoir of chronically infected Americans who can serve as a source of transmission to others and who are at risk of the severe consequences of chronic liver disease.

**Educational Objectives:** After completing this activity, the participant should be better able to:

1. Discuss the limitations of currently approved therapies for chronic hepatitis C.
2. Describe the potential role of protease and polymerase inhibitors in the treatment of hepatitis C.
3. Summarize the latest data regarding the efficacy of various protease/polymerase regimens for hepatitis C viral eradication.

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# Introduction

**H**epatitis C is a blood-borne liver disease triggered by infection with the hepatitis C virus (HCV). Many patients with acute HCV infection experience no symptoms, and the viral infection is cleared within two to three months.<sup>1</sup> However, 75–85% of individuals with HCV progress to chronic infection, defined as a persistence of infection for more than six months.<sup>2,3</sup> Individuals with chronic hepatitis C (CHC) infection have a greater risk for the development of serious disease complications, including cirrhosis and hepatocellular carcinoma (HCC). Today, CHC-related cirrhosis is the leading indication for liver transplantation.<sup>4</sup> The complications associated with decompensated cirrhosis include ascites, jaundice, variceal bleeding, and encephalopathy. Studies in cohorts of European CHC patients show a rate of decompensated liver disease development of approximately 4% per year, and a median risk of 3% per year for the development of HCC.<sup>1,5-7</sup>

Worldwide, hepatitis C infection is estimated to affect 120 million people.<sup>1,8</sup> According to the most current and ongoing National Health and Nutrition Examination Survey (NHANES) of 15,079 serum samples in the United States, 1.6% of individual samples expressed antibodies to HCV.<sup>9</sup> This corresponds to approximately 4.1 million people who were or had been infected with HCV, making HCV the most pervasive blood borne infection in the U.S. Additionally, nearly 80% of the anti-HCV positive serum samples also contained HCV RNA, translating to an estimated 3.2 million Americans with chronic HCV infection. Of the six distinct HCV genotypes which have been identified, genotype 1 is the most prevalent in the United States, accounting for over 70% of infections.<sup>9</sup> Although genotype is not associated with disease presentation or severity, it does influence response to antiviral therapy.<sup>10,11</sup>

The most frequent mode of HCV transmission in the U.S. is injection drug use, followed by sexual transmission.<sup>12,13</sup> Other less common modes of HCV transmission include perinatal transmission to infants and transmission in health care settings. Although historically important, transmission via blood transfusion is rare due to the routine testing of blood contributions for the presence of HCV RNA and anti-HCV antibodies.<sup>14</sup>

## Current Treatment of Chronic Hepatitis C

The primary goal of treating patients with CHC is to achieve a sustained virologic response (SVR), defined as having undetectable levels of HCV RNA 6 months following the end of therapy.<sup>15</sup> In recent years, a rapid virologic response (RVR), defined as having undetectable

HCV RNA levels at week 4 after the initiation of therapy, has been shown to be an important factor predictive of attaining an SVR.<sup>16</sup>

Presently, the standard therapy for CHC patients is a combination of interferon alfa, a cytokine with both antiviral and immune-activating properties, and ribavirin, a nucleoside analogue. Pegylated interferon (peg-IFN), a chemically modified version of interferon with a PEG polymer attached, has superior pharmacodynamic properties, allowing for improved solubility, extended half-life, and increased stability over the native interferon molecule.<sup>17</sup> Peg-IFN is administered subcutaneously, whereas ribavirin is given orally. In patients infected with genotype 1 HCV, this combination treatment achieves SVR rates of approximately 40–45%, and over 80% in patients with genotypes 2 or 3.<sup>18-20</sup> Because of its lower efficacy in patients with genotype 1, these individuals are recommended to continue treatment for 48 weeks, whereas patients with genotype 2 or 3 show no additional benefit with more than 24 weeks of therapy. Importantly, patients with a RVR may be able to achieve a SVR with a shorter duration of therapy, although this still remains controversial.<sup>21,22</sup>

This standard combination therapy is associated with a myriad of adverse effects. The most frequent adverse effects reported with ribavirin use are hemolysis and anemia. Peg-IFN can routinely cause fatigue, muscle aches, and flu-like symptoms, as well as bone marrow depression. Additionally, Peg-IFN administration is associated with an increased risk for psychological disorders, ranging from depression, anxiety, and irritability to sleep disorders. Patients experiencing these side effects are often likely to adhere less to therapy, thereby reducing the probability of achieving an SVR. Adverse effects induced by this standard combination treatment leads to premature therapeutic withdrawal in 10-20% of patients, with 20–30% more requiring dose modification.<sup>23</sup>

## Advances in Chronic Hepatitis C Therapy

Recently, the development of a cell-culture model of an HCV clone able to infect and replicate in hepatocyte-derived cell lines has allowed for the further discovery and development of novel agents, which target the replicative and infective ability of the virus.<sup>24-26</sup> Efforts to develop new therapeutic agents for the treatment of CHC are currently focused on inhibition of the viral enzymes necessary for the HCV to replicate, including the HCV protease and polymerase.<sup>27</sup> The most problematic feature of these novel targeted therapies is the generation of resistance mutations.<sup>27</sup> These mutations,

which occur in the viral genome, lead to changes in the amino acid sequence causing the viral variant to become resistant to the effects of the drug. HCV variants emerge as a result of selective pressure induced by the presence of the antiviral agent alone. Therefore, a combination of polymerase and protease inhibitors, or a combination with Peg-IFN, may avoid the generation and emergence of these resistant variants.

One of the most clinically advanced of these antiviral agents currently under investigation is the orally administered drug telaprevir (VX-950). Telaprevir is a potent HCV protease inhibitor, capable of reducing HCV RNA levels by 4.7 log<sub>10</sub> in cell-based studies.<sup>28</sup> Additionally, preclinical experiments in mice revealed that telaprevir inhibits the HCV protease in the liver, and achieved a favorable pharmacodynamic profile.<sup>29</sup> An initial phase I placebo-controlled trial demonstrated that telaprevir was well tolerated in patients with CHC.<sup>30</sup> Telaprevir monotherapy demonstrated antiviral activity in these patients, including individuals who had failed prior treatment. Another study, designed to evaluate the safety and viral kinetics of telaprevir either alone or in combination with Peg-IFN, reported mainly mild adverse effects with no premature discontinuation from therapy.<sup>31</sup> This study confirmed the potent antiviral effects of telaprevir in CHC patients, and additionally showed that these effects were enhanced when combined with Peg-IFN. A detailed analysis of the viral kinetics during telaprevir therapy revealed that the initial antiviral response was attributed to a potent inhibition of wild-type HCV.<sup>32</sup> Telaprevir monotherapy resulted in the selection for HCV variants with telaprevir-resistant mutations, but the additional combination of Peg-IFN inhibited the replication of these variants, reducing the incidence of viral rebound. Telaprevir is currently under continued investigation in the PROVE trials, a series of three phase II clinical studies designed to evaluate the safety and efficacy of different durations of telaprevir-based regimens.<sup>33</sup>

Another oral protease inhibitor under clinical evaluation is boceprevir (SCH-503034). In preclinical studies, boceprevir displayed potent inhibition of the HCV protease, resulting in a more than 4 log<sub>10</sub> reduction of HCV RNA in the in vitro HCV replicon system.<sup>34</sup> The efficacy of boceprevir in vitro was further enhanced in combination with interferon. In a multi-center phase I study, when combined with Peg-IFN, boceprevir was well tolerated and displayed antiviral activity.<sup>35</sup> Significantly, this activity occurred in patients who were classified as having no response to previous treatment with standard Peg-IFN plus ribavirin therapy. Further evaluation of boceprevir is ongoing in phase II trials.<sup>36</sup>

Several HCV polymerase inhibitors are also currently in clinical trials. Valopicitabine (NM-283) produced robust decreases in HCV RNA when combined with Peg-IFN, but

phase I and II studies reported gastrointestinal toxicities at a valopicitabine dose of 800 mg per day.<sup>37-39</sup> After some further research at a reduced dose, the manufacturer has elected to halt research into the use of valopicitabine. A second polymerase inhibitor, R1626, showed significant antiviral activity in a phase IIa study.<sup>40</sup>

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# Novel Protease and Polymerase Inhibiting Agents to Treat Chronic Hepatitis C Infection

A Review of Selected Presentations From the 58th Annual Meeting of the American Association for the Study of Liver Diseases November 2–6, 2007  
Boston, Massachusetts

## 1309 Final Results of Patients Receiving Peg-Interferon Alfa-2a (Peg-IFN) and Ribavirin (RBV) After a 14-Day Study of the Hepatitis C Protease Inhibitor Telaprevir (VX-950), With Peg-IFN

CJ Weegink, N Forestier, PL Jansen, S Zeuzem, HW Reesink

The efficacy of telaprevir in CHC patients has been established in multiple phase I clinical trials. In one study, single-agent telaprevir was administered at 3 doses over a course of 14 days.<sup>1</sup> When compared to placebo, telaprevir exhibited substantial antiviral activity, with median reductions in HCV RNA viral load of 4.4 log<sub>10</sub> at the highest dose. The rapid antiviral activity of telaprevir was further shown to be enhanced when combined with Peg-IFN in a separate phase I study.<sup>2</sup>

A third phase I study, VX05-950-103, was designed to evaluate the kinetics of HCV infection after telaprevir therapy. In this study, treatment-naïve, genotype 1 patients were randomly assigned to one of three treatment arms—either telaprevir alone (n=8), telaprevir plus Peg-

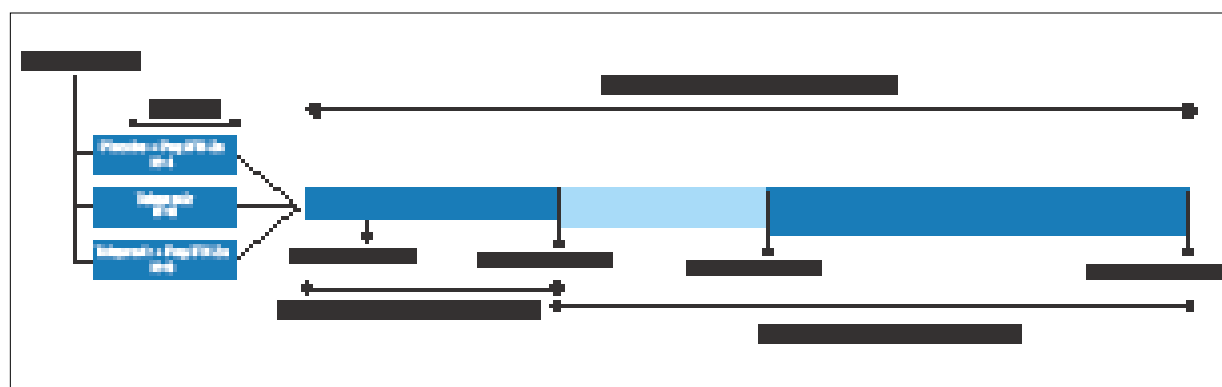
IFN-2a (n=8), or a control arm consisting of placebo plus Peg-IFN-2a (n=4). Telaprevir was administered orally (750 mg tablets every 8 hours), and Peg-IFN-2a was delivered subcutaneously on days 1 and 8. At the completion of the study dosing period, which lasted 14 days, patients were offered continued therapy with a standard regimen of Peg-IFN-2a plus ribavirin. All but 1 patient (n=19) opted to initiate this therapy within 5 days after completing the randomized portion of the study. A previous report summarized the antiviral and clinical effects of the initial 14 day treatment period, with a 12 week follow-up evaluation.<sup>3</sup> Patients who received telaprevir in combination with Peg-IFN-2a exhibited a superior reduction in HCV RNA levels, with a median decrease of 5.5 log<sub>10</sub> from baseline. This was a greater reduction than that seen in patients receiving either telaprevir alone (median decrease 4.0 log<sub>10</sub>) or Peg-IFN-2a plus placebo (median decrease 1.0 log<sub>10</sub>).

In this current analysis, Weegink and associates summarized the final results of the extended off-study treatment portion of this trial, during which patients received standard therapy with Peg-IFN-2a and ribavirin.<sup>4</sup> Throughout the off-study period, patient HCV RNA levels were assessed at both a 24-week and 48-week follow-up.

At the initial 12 week follow-up, 5 of the 7 patients who had received telaprevir alone and all 8 patients who had

**Table 1.** VX05-950-103: Undetectable HCV RNA by Groups During Off-study Treatment With Peg-IFN-2a and RBV and at Follow up.

	Number of patients with undetectable HCV RNA (< 10 IU/mL)					
	Week 12	Week 24		Week 48		Week 72 SVR Total
VX-950 (N=7)	5	7	4 stop treatment, 2 relapse	5	1 relapse	4
VX-950/Peg-IFN-2a (N=8)	8	8	6 stop treatment, 1 relapse	7	1 relapse	6
Peg-IFN-2a (N=4)	1	3		3	2 relapse	1



**Figure 1.** VX05-950-103 clinical study design.

received telaprevir plus Peg-IFN-2a achieved undetectable levels of HCV RNA (<10 IU/ml). In contrast, only 1 of the 8 patients receiving Peg-IFN-2a alone had undetectable HCV RNA levels at this same time point. By week 24, all of the patients in both telaprevir-containing arms achieved undetectable HCV RNA levels, and 3 patients in the Peg-IFN-2a plus placebo arm did. At this point, 10 patients from the two telaprevir arms stopped the off-study therapy with Peg-IFN-2a and ribavirin. Of these, 2 of the 4 patients in the telaprevir-only arm relapsed, and 1 of the 6 patients in the telaprevir plus Peg-IFN-2a arm relapsed. The remaining patients in each group stopped therapy at 48 weeks (n=3 for the telaprevir only group and n=2 for the telaprevir plus Peg-IFN-2a group). Virologic relapse occurred in 1 patient from the telaprevir-only arm and in 1 patient from the telaprevir combination arm. At week 72, this resulted in an SVR in 4 of 7 patients in the telaprevir-only arm, 6 of 8 patients in the telaprevir plus Peg-IFN-2a arm, and 1 of 4 patients in the Peg-IFN-2a only arm (Table 1 and Figure 1).

In the 5 total patients from both telaprevir-based treatment groups who relapsed, HCV RNA sequence

analysis was performed to determine the extent of the emergence of viral variants. In 3 of these samples, mutations known to confer telaprevir resistance were found.<sup>5</sup> The viral variants identified in these patients included mutations at V36, A156, and R155. The other 2 patient samples contained only wild-type sequence.

During post-study therapy with the Peg-IFN-2a plus ribavirin combination, safety evaluations revealed no new or unusual adverse events that were not typically associated with this treatment. The final conclusions from this report found that all patients receiving telaprevir, either alone or in combination with Peg-IFN, and continued on Peg-IFN plus ribavirin standard therapy, maintained undetectable levels of HCV RNA through week 24. The authors noted that the extended follow-up SVR data from this study were similar to models which predict that a durable SVR is related to early viral clearance, evident by the antiviral response observed in patients after the preliminary 14-day telaprevir treatment. Although this study was limited by a small patient sample size, larger studies are underway to confirm the long-term safety and efficacy of telaprevir.

## 177 Interim Analysis Results From a Phase II Study of Telaprevir With Peg-Interferon Alfa-2a and Ribavirin in Treatment-Naïve Subjects With Hepatitis C

IM Jacobson, GT Everson, SC Gordon, R Kauffman, L McNair, A Muir, JG McHutchison

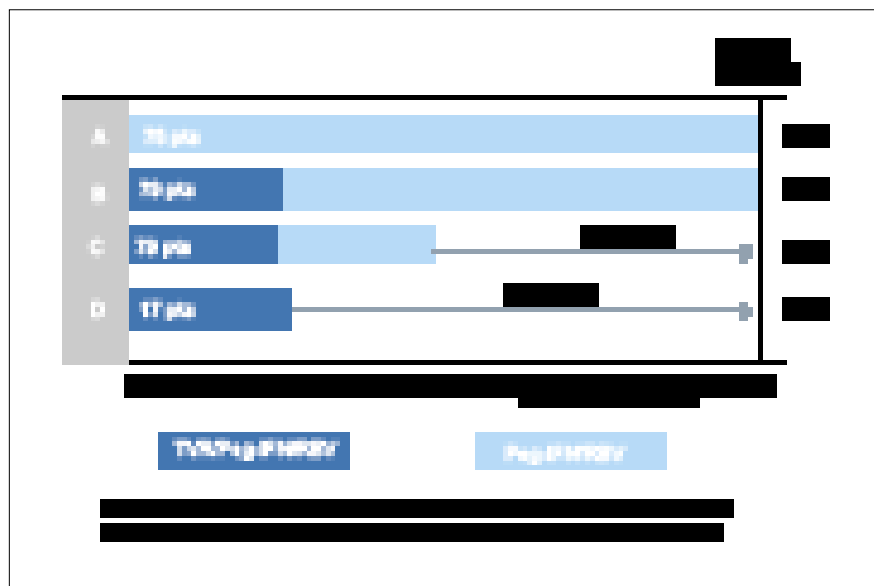
Successful completion of several phase I studies evaluating the safety and efficacy of telaprevir in patients with CHC has led to phase II clinical development. Recently, a series of three phase II clinical trials were initiated, designed to investigate different durations and combinations of telaprevir-based regimens. These studies, termed the PROVE trials, are fully enrolled and ongoing.<sup>6</sup> Here, Jacobson and colleagues report the results from a planned interim analysis of the PROVE 1 trial.<sup>7</sup> PROVE 1 is a randomized, placebo-controlled study with four treatment arms consisting of various therapeutic durations.

All of the patients enrolled in the PROVE 1 study had genotype 1 CHC infection, with no evidence of cirrhosis, and had received no prior therapy. The majority of patients were Caucasian and male, and patient characteristics were evenly distributed across all four treatment arms. A total of 250 patients were randomly assigned to four treatment arms (Figure 2). Three groups received an initial 12 week administration of a triple combination of telaprevir (750 mg every 8 hours), Peg-IFN-2a (180 mg weekly), and ribavirin (1000–1200 mg per day). This was followed by either 0 (n=17), 12 (n=79), or 36 (n=79) weeks of a follow-up combination therapy consisting of continued doses of Peg-IFN-2a plus ribavirin. A fourth group of patients

(n=75) were randomized to a control arm, consisting of the initial 12 week combination with placebo substituted for telaprevir. This was subsequently followed by 36 weeks of the Peg-IFN-2a and ribavirin combination. This current report evaluated interim data from all patients at 48 weeks after the initiation of therapy.

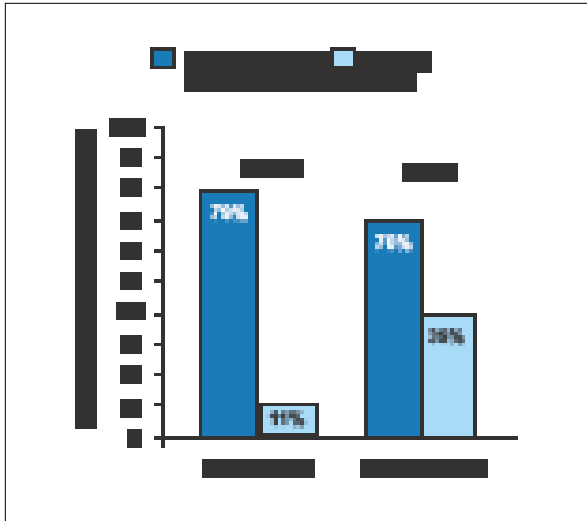
Therapeutic efficacy was assessed by measuring plasma HCV RNA levels. Viral loads were determined both at baseline and during treatment using the Taqman HCV RNA assay, a quantitative real-time polymerase chain reaction-based technique. Both at weeks 4 and 12, a significantly larger percentage of patients in the three combined telaprevir groups (n=175) showed undetectable levels of HCV RNA (<10 IU/ml), when compared to the placebo-controlled group (Figure 3). At week 4, 79% of patients in the combined telaprevir arms had achieved undetectable HCV RNA levels, compared to only 11% in the placebo group ( $P<.001$ ). Similarly, 70% of all of the telaprevir-receiving patients had undetectable levels of HCV RNA at week 12, versus 39% of the placebo-receiving patients ( $P<.001$ ). Importantly, 91% of the patients receiving telaprevir achieved undetectable HCV RNA levels at some point during the first 12 weeks of therapy.

During the first 12 weeks of therapy, 14 patients experienced a viral breakthrough, defined as an increase in HCV RNA of either greater than 100 IU/mL after having been measured undetectable, or a 1 log<sub>10</sub> increase from nadir. Of these 14 patients, 2 were in the placebo-controlled group, and the remaining 12 were in the combined telaprevir groups. All but 1 of these 12 viral breakthroughs occurred during the first 4 weeks of therapy, and 9 occurred in patients who had never



**Figure 2.** PROVE1 study design.

EOT=end of treatment;  
HCV=hepatitis C virus;  
RBV=ribavirin; RVR=rapid virologic response;  
SVR=sustained virologic response; TVR=telaprevir.



**Figure 3.** PROVE1: telaprevir-receiving groups had significantly better antiviral response a Week 4 and Week 12.

ITT=intent to treat; TVR=telaprevir.

achieved undetectable levels of HCV RNA. After the plasma HCV RNA was isolated and sequenced from these 12 patients, all were found to express a high level of viral variants known to be resistant to telaprevir. Additionally, viral breakthrough more often occurred in patients who attained lower plasma concentrations of both telaprevir and Peg-IFN-2a.

The rates of SVR at 48 weeks after initiation of therapy were determined for the two shorter duration treatment groups, the telaprevir arms receiving either 0 or 12 additional weeks of standard therapy. Patients who continued therapy with Peg-IFN and ribavirin following the initial telaprevir-based 12-week triple combination regimen achieved superior rates of SVR, compared to patients who did not receive continued therapy (61% versus 35%, respectively). Because this 48-week interim analysis occurred before an SVR could be measured in the longest treatment groups, an end-of-treatment analysis was performed on these patients. This analysis included patients in both the placebo-controlled arm and the telaprevir plus 36 weeks standard therapy arm, which

were both completed at 48 weeks. When these two groups were directly compared, a larger percentage of patients in the telaprevir group compared to the placebo group achieved undetectable HCV RNA levels (65% versus 45%, respectively). Therefore, analysis of both SVR and end-of-treatment response determined that the addition of telaprevir to the standard treatment regimen resulted in more potent antiviral activity, as does continued dosing with the standard therapy after termination of telaprevir.

The number of patients who experienced a virologic relapse after having achieved undetectable HCV RNA levels at the end of telaprevir-based treatment was inversely correlated with the total duration of therapy. After receiving a total duration of 24 weeks of therapy, 42 patients achieved undetectable HCV RNA levels, and only 1 (2.4%) experienced a relapse after treatment. This number went up to 3 of 9 patients (33%) and 12 of 19 patients (63%) in patients who had either 12 weeks or less than 12 weeks total duration of therapy, respectively.

In this study, the most frequently reported adverse effects were those expected with Peg-IFN and ribavirin therapy, including fatigue, flu-like illness, and headache. Telaprevir was associated with more frequent reports of rash, pruritus, anemia, and gastrointestinal events such as nausea, diarrhea, and vomiting. A total of 12 patients from the three telaprevir groups combined discontinued therapy due to rash or pruritus, compared to only 1 in the control group. Anemia led to 3 discontinuations in the combined telaprevir groups and no discontinuations in the control group, and gastrointestinal effects induced discontinuation of treatment in 5 of the combined telaprevir arms compared to 1 in the control group.

This interim data from the PROVE1 study offered further evidence that telaprevir induces a high rate of RVR in CHC patients, with a majority of patients exhibiting on-treatment viral response within 4 weeks of therapy. Telaprevir therapy was also associated with a low rate of viral relapse, and a low risk of viral breakthrough. The study investigators suggested that telaprevir has the potential to produce higher rates of SVR compared to the current standard treatment regimen, and the RVR induced by telaprevir may allow patients to receive a shorter duration of therapy.



## 80 PROVE2: Phase II Study of VX950 (Telaprevir) in Combination With Peg-Interferon Alfa-2a With or Without Ribavirin in Subjects With Chronic Hepatitis C, First Interim Analysis

C Hezode, P Ferenci, GM Dusheiko, S Pol, T Goeser, JP Bronowicki, S Gharakhanian, D Devonish, R Kauffman, J Alam, JM Pawlowsky, S Zeuzem

## LB8 Evaluation of Viral Variants During a Phase II Study (PROVE2) of Telaprevir With Peg-Interferon Alfa-2a and Ribavirin in Treatment-Naive HCV Genotype 1-Infected Patients

T Kieffer, Y Zhou, E Zhang, M Marcial, R Byrn, T Pfeiffer, J Miller, A Tigges, D Bartels, A Kwong, P Ferenci, G Dusheiko, S Zeuzem, JM Pawlowsky

Results from the first interim analysis of the PROVE 2 trial, the second in the PROVE series of randomized and placebo-controlled phase II clinical studies evaluating telaprevir in patients with CHC, were presented in two separate reports. In the first report, the clinical results of the interim analysis are summarized, whereas the second analysis describes the viral variants responsible for telaprevir resistance in the PROVE 2 patient population.

The PROVE 2 study enrolled 323 treatment-naive CHC patients with genotype 1 infection. The majority of patients were Caucasian males, with a median age of 44–45 years. Patients were randomized into four treatment arms. The control arm (n=82) received 48 continuous weeks of standard therapy, consisting of Peg-IFN-2a combined with ribavirin. The second group (24-week arm) received a triple combination of telaprevir, Peg-IFN-2a, and ribavirin for 12 weeks, followed by 12 weeks of Peg-IFN-2a and ribavirin alone. The third group (12-week arm) received the same initial 12 week triple combination therapy, but had no subsequent follow-up treatment with Peg-IFN-2a and ribavirin. The fourth arm received no ribavirin (no ribavirin arm), and instead was administered telaprevir in combination with Peg-IFN-2a only for 12 weeks, followed by no additional follow-up therapy. In this study, 750 mg of telaprevir or its placebo was administered orally every 8 hours. Peg-IFN-2a was delivered weekly (180 mg) and ribavirin was given daily (1000–1200 mg). The interim analysis reported here occurred at 36 weeks after the initiation of treatment, and

included the intent-to-treat population of patients who received at least one dose of the intended study drug in their particular treatment arm.<sup>8</sup>

Prior to the week 12 assessment, 15%, 13%, and 10% of patients in the 24-week, 12-week, and no ribavirin arms respectively, discontinued treatment. The majority of these discontinuations were attributed to adverse effects, with skin and gastrointestinal events occurring more commonly in patients receiving telaprevir. One of the most notable skin effects, a maculopapular rash, was reported to be a typical reaction to telaprevir that was resolved once therapy was discontinued. Although it had no effect on either neutrophil or platelet counts, patients receiving telaprevir also had an increased incidence of anemia, the majority of which were grade 1. The remaining frequently reported adverse effects were those expected to occur from Peg-IFN-2a and ribavirin treatment.

Telaprevir therapy resulted in undetectable HCV RNA levels (<10 IU/mL) in a significantly greater number of patients compared to the placebo-receiving control group (Figure 4). At week 4, compared to 13% of the control group, 69%, 80%, and 51% of patients in the 24-week, 12-week, and no ribavirin arms respectively achieved undetectable HCV RNA levels ( $P<.001$  for all groups compared to the control arm). By week 12, all three telaprevir-receiving groups (73%, 79%, and 62%) continued to exhibit significantly superior rates of undetectable HCV RNA levels compared to 41% of the control group ( $P<.001$  for all treatment arms compared to control).

Of the patients in the 24-week arm, 65% achieved an SVR at 12 weeks after treatment completion. Similarly, 59% of patients in the 12-week arm achieved an SVR, determined at 24 weeks following completion of therapy. A lower percentage of patients (29%) in the no ribavirin arm had an SVR at 24 weeks following completion of therapy. Determination of the rate of SVR in the control arm is still on-going.

Patients who received the longer total duration of therapy in the 24-week arm had a lower rate of viral relapse compared to those who received the shorter duration of therapy in the 12-week arm (14% versus 28%, respectively). Importantly, attaining an RVR was predictive of a lower risk of relapse. In the 24-week treatment arm, only 11% of patients who achieved an RVR went on to experience a viral relapse, compared to 30% of patients who did not exhibit an RVR. Similar results were also shown in the 12-week treatment arm, where only 22% of patients achieving an RVR had a viral relapse, compared to 75% of patients who did not have an RVR.

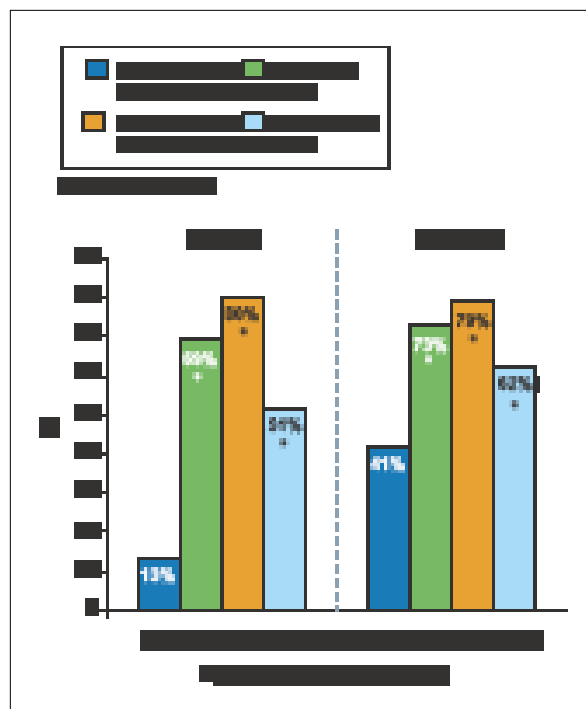
The inclusion of ribavirin was found to be an important determinant of the risk of viral breakthrough

during the first 12 weeks of therapy. In this study, viral breakthrough was defined as an increase in HCV RNA while on treatment, either as an increase of greater than 100 IU/mL in patients who had previously undetectable levels, or an increase of greater than 1 log<sub>10</sub> over nadir. Compared to 1% in the control group and 2% in the 12-week and 24-week telaprevir arms combined (5% in the 24-week arm; 0% in the 12-week arm), 24% of patients in the no ribavirin arm exhibited a viral breakthrough. The dramatic increase in viral breakthrough that occurred in patients in the no ribavirin arm suggested that the inclusion of ribavirin with the treatment regimen is necessary to decrease the risk of the emergence of telaprevir-resistant viral variants. Sequence analysis of the HCV RNA in these patients was performed to determine viral variants, and this data was reported in a second abstract, presented by Kieffer and fellow investigators.<sup>9</sup>

At baseline, sequence analysis revealed that the vast majority (99%) of the patient samples expressed wild-type virus (316 of 320 patients). In the remaining 4 patients, 3 (1%) had the V36M variant, and 1 (0.3%) expressed the R155K variant. Interestingly, an initial response to therapy was observed in 3 of these patients, and 2 who received telaprevir achieved a SVR at 24 weeks following therapy (the remaining patient was in the control group). Wild-type HCV was shown to be effectively cleared after 8 weeks of the telaprevir, Peg-IFN-2a, and ribavirin regimen. Additionally, variants with a lower-level of telaprevir resistance were cleared in many patients after 12 weeks of this triple combination therapy.

A phenotypic analysis of the telaprevir resistant variants determined the level of resistance incurred by each mutation. This was measured by the change in the in vitro telaprevir IC<sub>50</sub> against each variant. Compared to wild-type, each individual mutation conferred an increased resistance of 6-fold (T54A), 7-fold (V36A/M or R155K), 10-fold (A156S), 20-fold (R155T/I), greater than 60-fold (V36A/M plus R155K), and greater than 62-fold (A156V/T).

In the 12-week and 24-week telaprevir arms combined, the low rate of viral breakthrough (2%) mainly occurred early during treatment, with 3 of the 4 patients having viral breakthrough during the first 4 weeks. These viral breakthroughs were found to be associated with the variants having a higher level of resistance (V36A/M plus R155K, and A156V/T). None of these 4 patients ever achieved undetectable levels of HCV RNA. In contrast, the rate of viral breakthrough (24%) was much higher in the no ribavirin arm. Many of these breakthroughs (9 of 19) occurred early, during the first 4 weeks of treatment, and the viral breakthroughs were associated with both lower and higher level resistance variants. The majority of these patients (n=16) never achieved undetectable HCV RNA levels.



**Figure 4.** PROVE2: undetectable HCV RNA at Weeks 4 and 12.

Interestingly, sequence analysis further showed that continuing telaprevir therapy after the occurrence of a viral breakthrough allowed for the selection of additional viral variants with multiple telaprevir resistance mutations. For example, in one patient who experienced a viral breakthrough, sequencing revealed the emergence of the A156V/T variant within the first 4 weeks of therapy. Over the course of continued telaprevir treatment, other variants emerged, including the R155K variant followed by the V36M plus R155K variant. Consequently, HCV RNA levels continued to increase in response to the emergence of these variants. Based on these observations, the study authors suggested that once a viral breakthrough is observed, telaprevir therapy should be discontinued in order to prevent the selection of further resistance mutations. Importantly, once selective pressure was halted when telaprevir treatment was discontinued, viral sequencing revealed that wild-type virus replaced the mutated virus in some patients. This was likely due to a decreased replicative fitness of the telaprevir-resistant viral variants.

These first interim results from the ongoing PROVE 2 trial showed the antiviral activity of multiple telaprevir-based regimens in patients with CHC. Patients who received telaprevir were significantly more likely to achieve undetectable levels of HCV RNA. This was evident as early as week 4 of therapy, indicating the ability of telaprevir to induce an RVR. Additionally,

achieving an RVR was associated with a decreased risk of virologic relapse. Sequence analysis of patients exhibiting a viral breakthrough revealed the emergence of telaprevir-resistant viral variants. A significant finding of this first interim analysis was that the inclusion of ribavirin in the telaprevir-based treatment regimen was an important determinant in the rate of viral breakthrough. The authors of both of these reports concluded from this data that the addition of telaprevir to the current standard regimen of Peg-IFN plus ribavirin may potentially result in increased efficacy leading to higher rates of SVR over the standard combination alone.

### 1391 HCV Polymerase (NM107) and Protease (Boceprevir) Inhibitors in Combination Show Enhanced Activity and Suppression of Resistance in the Replicon System

DN Strandring, V Bichko, R Chase, M LaColla, L Lallo, A Skelton, M Soukasakos, M Tausek, X Tong, R Ralston

When a polymerase and a protease inhibitor are combined, the protease inhibitor may be active in virions with resistance to the polymerase inhibitor, while the polymerase inhibitor can act on virions with resistance to the protease inhibitor. This would result in increased antiviral activity compared to each single agent administered alone.

One such combination under investigation is the administration of valopicitabine (NM-283), an investigational nucleoside polymerase inhibitor, with boceprevir (SCH-503034), an investigational protease inhibitor. Each of these agents as monotherapy have demonstrated antiviral activity against HCV in both preclinical and clinical studies.<sup>10,11</sup> Additionally, both valopicitabine and boceprevir display increased efficacy when combined with Peg-IFN.<sup>12-14</sup> Here, Strandring and colleagues used *in vitro* cell culture replicon assays to evaluate these agents in combination.<sup>15</sup>

In this study, genotype 1b HCV replicon cells were treated with both valopicitabine and boceprevir in combination. The antiviral effect of both agents together was evaluated by real-time reverse transcription-polymerase chain reaction and an enzyme-linked immunosorbent assay. Combination of valopicitabine with boceprevir resulted in an increase in replicon inhibition, compared to the effect of each agent alone. Notably, this replicon inhibition occurred in a dose-dependent manner, and no cytotoxicity was observed.

Neither drug displayed evidence of cross-resistance, assayed using replicon variants that expressed single

protease inhibitor (T54A, A156S, V170A, or A156T) or polymerase inhibitor (S282T) resistance mutations.<sup>16,17</sup> Valopicitabine had similar antiviral activity against both wild-type and boceprevir-resistant replicons, with a half maximal effective concentration (EC<sub>50</sub>) of 1.5–2 mM. Likewise, boceprevir displayed similar antiviral activity against both the wild-type and valopicitabine-resistant replicons, with an EC<sub>50</sub> of 0.3–0.4 mM. In contrast, when evaluated against their respective known resistance mutations, each agent exhibited a 5- to 125-fold loss in susceptibility. Importantly, combination of valopicitabine with boceprevir reduced the frequency of the emergence of resistant replicons in a dose-dependent manner, when compared to each antiviral agent alone.

This study provided evidence that the combination of these individual polymerase and protease inhibitors increased their ability to inhibit replicons over each agent alone. Importantly, this combination was active without evidence of cross-resistance, and in fact produced a greater genetic barrier to resistance. The authors of this study suggested that clinical evaluation of this combination should subsequently be performed in patients with chronic HCV infection, in order to confirm these *in vitro* results.

### LB15 Efficacy and Safety of Valopicitabine in Combination with Pegylated Interferon- $\alpha$ (Peg-IFN) and Ribavirin (RBV) in Patients with Chronic Hepatitis C

F Poordad, EJ Lawitz, N Gitlin, M Rodriguez-Torres, T Box, T Nguyen, K Pietropaolo, W Liu, BA Fielman, D Mayers

A second study, presented by Poordad and fellow authors, evaluated the polymerase inhibitor valopicitabine in combination with the standard anti-HCV treatment regimen of Peg-IFN with ribavirin.<sup>18</sup> This study included 117 patients with genotype 1 HCV and compensated liver disease who had not received any prior therapy. Patients were randomly assigned to three treatment arms. Patients in the first arm received 200 mg valopicitabine per day plus 180 mg Peg-IFN-2a every week, whereas patients in the second arm received this same treatment, with the addition of 1000–1200 mg ribavirin per day. The third group of patients received 1000–1200 mg ribavirin daily plus 180 mg Peg-IFN-2a every week, and placebo in place of valopicitabine. Valopicitabine (or its placebo) was administered for 1 week prior to the initiation of Peg-IFN-2a on day 8 with or without ribavirin. This treatment regimen was continued for 12 weeks, after which patients then received 36 weeks of the standard therapy of Peg-IFN-2a plus ribavirin.

No pharmacokinetic drug interactions were observed between valopicitabine and ribavirin. An analysis of as-treated patients showed a mean difference in HCV RNA between the triple combination group and the no valopicitabine group of 0.45–0.66 log<sub>10</sub> IU/mL, which was maintained at each study evaluation. When analyzed as treated, patients in the triple combination group displayed superior rates of HCV RNA PCR-negativity at weeks 4, 8, and 12 (16%, 56%, 72%, respectively) compared to patients in the no valopicitabine arm (5%, 37%, 62%, respectively) and Peg-IFN-2a plus valopicitabine arm (11%, 33%, 44%, respectively). Comparatively, the intent-to-treat analysis revealed HCV RNA-negativity rates at week 12 of 67%, 62%, and 44% for the triple combination, no valopicitabine, and Peg-IFN-2a plus valopicitabine arms, respectively.

A safety evaluation revealed that 3 patients discontinued therapy early. All 3 of these individuals had received the triple combination therapy. One serious adverse event was attributed to Peg-IFN-2a in a triple combination recipient. Gastrointestinal-related adverse events were reported in 77% of patients receiving the triple combination regimen, compared to 67% of the Peg-IFN-2a plus valopicitabine group and 49% of the no valopicitabine group. Patients receiving valopicitabine also experienced mean increases in several enzymes, including aspartate aminotransferase, creatine kinase, pancreatic amylase, and lipase. However, these increases were not associated with the occurrence of any clinical adverse events, and by the end of treatment, both aspartate aminotransferase and creatine kinase enzymatic levels decreased in patients in the triple combination arm.

Despite the antiviral activity demonstrated by valopicitabine in this and other phase II studies, its use results in significant adverse effects including gastrointestinal toxicity. In an effort to reduce these effects, this study used a lower dosage of valopicitabine (200 mg) compared to the higher dose of 800 mg administered in earlier phase I studies. Although the adverse effect profile was improved, considerable gastrointestinal toxicity was still observed. Based on these results and the overall risk-to-benefit from previous trials, the continued clinical testing of valopicitabine has been halted.<sup>19</sup>

## 167 Robust Synergistic Antiviral Effect of R1626 in Combination With Peginterferon Alfa-2a (40KD), With or Without Ribavirin—Interim Analysis Results of Phase 2A Study

PJ Pockros, D Nelson, E Godofsky, M Rodriguez-Torres, G Everson, MW Fried, RH Chalib, SA Harrison, LM Nyberg, ML Shiffman, GZ Hill, A Chan

R1626 is another potent HCV polymerase inhibitor that has shown promise in CHC patients. When administered as monotherapy, R1626 demonstrated the capacity to effect dose-dependent decreases in HCV RNA.<sup>20</sup> Pockros and associates conducted this phase II study to determine the safety and efficacy of 2 different dosing regimens of R1626 administered in combination with various regimens of Peg-IFN-2a and ribavirin for 4 weeks only.<sup>21</sup> As in the PROVE trials, all patients enrolled were genotype 1 and treatment-naive. Patients were randomized to R1626, 1500 mg twice daily, in combination with standard-dose Peg-IFN-2a (dual-low arm); R1626, 3000 mg twice daily with standard-dose Peg-IFN-2a (dual-high arm); 1500 mg R1626 with standard dose Peg-IFN-2a and ribavirin (triple-low arm); or standard-of-care Peg-IFN-2a and ribavirin therapy.

At the end of 4 weeks, 81% of patients in the triple-low arm had achieved undetectable HCV RNA levels, as had 69%, 33%, and 5% in the dual-high, dual-low, and standard-of-care arms, respectively. Out of the total patient population (n=104), 6 patients experienced a total of 8 serious adverse events. The most common adverse event requiring dose reduction was Grade 4 neutropenia, which was more common in the R1626 arms than in the standard-of-care only arm. The authors concluded that R1626 displays a robust synergistic effect with Peg-IFN-2a, both with and without ribavirin cotherapy and note that additional studies of varying doses in combination with standard care are underway.

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## Commentary

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As data from clinical trials of therapy for chronic hepatitis C continue to accrue, the importance of achieving complete viral suppression as quickly in the course of therapy as possible becomes increasingly clear. A rapid virologic response (RVR), defined as an undetectable HCV RNA after 4 weeks of therapy, correlates with achieving a sustained virologic response (SVR). Novel protease and polymerase inhibitors have great potential for increasing the likelihood of RVR and SVR as shown by studies presented at the 2007 meeting of the AASLD.

The protease inhibitor telaprevir is the next generation agent closest to being available for general use. Data

reported at the 2007 AASLD showed encouraging results when telaprevir is used in combination with the standard-of-care therapy—Peg-IFN and ribavirin. The trial reported by Weegink and colleagues demonstrated the potential of telaprevir to allow more rapid viral suppression and higher SVR rates than standard therapy, despite the study design allowing only 2 weeks of therapy with telaprevir followed by additional therapy with Peg-IFN and ribavirin.

The phase II PROVE trials provide additional encouraging data—results from both the PROVE 1 and PROVE 2 trials were presented. These study designs examined patients undergoing therapy in a variety of

novel scenarios: 12 weeks of triple therapy with telaprevir, Peg-IFN alfa-2a, and ribavirin as a complete course of therapy; twelve weeks of triple therapy followed by courses of standard therapy for 12 and 36 weeks; and telaprevir in combination with only Peg-IFN, no ribavirin. All of these permutations of therapy were compared with patients undergoing standard-of-care therapy with a Peg-IFN, ribavirin, and placebo.

The PROVE 1 trial showed that 12 weeks of triple therapy followed by 12 weeks of standard-of-care yielded an SVR of 61% in these naïve, genotype 1 patients without cirrhosis, seemingly an improvement over genotype 1 historical controls. A regimen of 12 weeks of triple therapy followed by 36 weeks of standard therapy yielded an end-of-treatment response (ETR) of 65%. The SVR for this group was not available at the time of the meeting but it would seem unlikely to be significantly better than the 12 week group suggesting no benefit from extending the standard therapy. The study arm of combination therapy with only telaprevir and Peg-IFN produced an SVR of only 29% and this arm had a significantly higher percentage of viral breakthrough illustrating the importance of ribavirin in these regimens. The PROVE 2 trial also suggested that triple therapy will yield an SVR rate of approximately 60% in naïve, non-cirrhotic, genotype 1 patients.

Another important point that came out of the PROVE 1 trial was the observation of an association between lower plasma concentrations of both telaprevir and Peg-IFN, the achievement of complete viral suppression, and the likelihood of viral breakthrough. In the telaprevir-administered arms, 12 patients developed viral breakthrough and were found to express a high level of viral variants known to be resistant to telaprevir. Of these patients, 11 developed breakthrough in the first 4 weeks of therapy and 9 of these patients never achieved an undetectable HCV RNA. Viral breakthrough more often occurred in patients who had lower plasma concentrations of Peg-IFN and telaprevir. This supports the importance of early viral kinetics and pharmacokinetics in achieving success with treatment.

The most common adverse events reported with telaprevir were a maculopapular rash, anemia, and GI events. Whether these side-effects will limit therapy remains to be seen in the phase III trial.

The use of a de novo combination of a protease and a polymerase inhibitor in combination with Peg-IFN presents an attractive scenario to increase SVR rates while

reducing the risk of viral breakthrough. Although severe gastrointestinal side effects have led the manufacturer to halt research of the polymerase inhibitor NM283, an in vitro study of this agent in combination with the protease inhibitor, boceprevir, provided proof of the principle that polymerase and protease inhibitors will have an additive effect on viral suppression while reducing the risk of emerging viral resistance.

In conclusion, triple therapy with telaprevir, Peg-IFN, and ribavirin for 12 weeks followed by standard combination therapy with Peg-IFN and ribavirin for an additional 12 weeks will provide higher rates of RVR and SVR than standard therapy. Boceprevir, a protease inhibitor, and R1626, a polymerase inhibitor, both have promising early results. The combination of a polymerase and protease inhibitor showed promise in an in vitro assay.

The days of a “one-size-fits-all” mentality for treating patients with chronic HCV are gone. While the coming availability of new agents will increase the response rate, clinicians must keep in mind that in chronic HCV there is a combination of host-immune and viral factors that can impact the individual response to any form of therapy. As such, each patient must be considered as an individual. Monitoring of each patient’s response to therapy, particularly in those critical early weeks, and reacting appropriately will be critical to optimizing a patient’s likelihood of success. The hepatology community looks forward to the opportunities and challenges that the new generation of agents will provide.

## Suggested Reading

Sulkowski MS. Specific targeted antiviral therapy for hepatitis C. *Curr Gastroenterol Rep.* 2007;9:5-13.

Forestier N, Reesink HW, Weegink CJ, et al. Antiviral activity of telaprevir (VX-950) and peginterferon alfa-2a in patients with hepatitis C. *Hepatology.* 2007;46:640-648.

Kempf DJ, Klein C, Chen HJ, et al. Pharmacokinetic enhancement of the hepatitis C virus protease inhibitors VX-950 and SCH 503034 by co-dosing with ritonavir. *Antivir Chem Chemother.* 2007;18:163-167.

Kemmer N, Neff GW. Managing chronic hepatitis C in the difficult-to-treat patient. *Liver Int.* 2007;27:1297-1310.

Kornberg A, Kupper B, Tannapfel A, et al. Antiviral maintenance treatment with interferon and ribavirin for recurrent hepatitis C after liver transplantation: Pilot study. *J Gastroenterol Hepatol.* 2007;22:2135-2142.

# Novel Protease and Polymerase Inhibiting Agents to Treat Chronic Hepatitis C Infection

**CME Post-Test:** Circle the correct answer for each question below.

- Successful SVR in the treatment of chronic HCV is defined by the undetectable measure of viral DNA \_\_\_ months after the completion of therapy.
  - 3
  - 6
  - 9
  - 12
- RVR in the treatment of chronic HCV is defined as achievement of undetectable viral DNA \_\_\_ weeks after the initiation of therapy.
  - 4
  - 6
  - 12
  - 18
- Adverse effects associated with standard HCV therapy lead to premature therapeutic withdrawal in \_\_\_ patients.
  - 5–10%
  - 5–15%
  - 10–20%
  - 30–40%
- The interim analysis of PROVE 1, reported by Jacobson and fellow investigators, showed that telaprevir produced a significant rate of RVR compared to the placebo control. When patients in all 3 telaprevir-receiving groups were combined, \_\_\_\_\_ achieved undetectable HCV RNA levels at week 4, compared to 11% in the control group.
  - 39%
  - 70%
  - 79%
  - 81%
- Interim results of the PROVE 2 trial, described by Hezode and colleagues, showed that at \_\_\_\_\_ of patients in the 24-week treatment group achieved undetectable HCV RNA levels at week 4.
  - 51%
  - 69%
  - 73%
  - 80%
- In the PROVE 2 study results, a RVR was predictive of a lower risk of relapse. In patients in the 12-week treatment group, only \_\_\_\_\_ of patients who achieved a RVR had a viral relapse, compared to \_\_\_\_\_ of patients who did not.
  - 11%; 30%
  - 31%; 72%
  - 11%; 45%
  - 22%; 75%
- Valopicitabine targets the HCV \_\_\_\_\_.
  - polymerase
  - protease
  - RNA
  - envelope
- Clinical investigation of valopicitabine has revealed it causes considerable \_\_\_\_\_.
  - anemia
  - hair loss
  - gastrointestinal toxicity
  - neutropenia
- In Pockros and associates' study of R1626 in combination with standard therapy, \_\_\_% of patients in the "triple-low arm" achieved undetectable HCV RNA.
  - 55
  - 62
  - 77
  - 81
- In the R1626 study, the most common dose-reduction-requiring adverse event associated with R1626 was \_\_\_\_\_.
  - depression
  - anemia
  - neutropenia
  - flu-like symptoms

# Evaluation Form: Novel Protease and Polymerase Inhibiting Agents to Treat Chronic Hepatitis C Infection

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:

1 = Strongly Disagree    2 = Disagree    3 = Neutral    4 = Agree    5 = Strongly Agree

## Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

- |  |   |   |   |   |   |
|--|---|---|---|---|---|
| 1. Discuss the limitations of currently approved therapies for chronic hepatitis C.  | 1 | 2 | 3 | 4 | 5 |
| 2. Describe the potential role of protease and polymerase inhibitors in the treatment of hepatitis C.                          | 1 | 2 | 3 | 4 | 5 |
| 3. Summarize the latest data regarding the efficacy of various protease/polymerase regimens for hepatitis C viral eradication. | 1 | 2 | 3 | 4 | 5 |

## Overall Effectiveness of the Activity

The content presented:

- |   |   |   |   |   |   |
|---|---|---|---|---|---|
| Was timely and will influence how I practice      | 1 | 2 | 3 | 4 | 5 |
| Enhanced my current knowledge base                | 1 | 2 | 3 | 4 | 5 |
| Addressed my most pressing questions              | 1 | 2 | 3 | 4 | 5 |
| Provided new ideas or information I expect to use | 1 | 2 | 3 | 4 | 5 |
| Addressed competencies identified by my specialty | 1 | 2 | 3 | 4 | 5 |
| Avoided commercial bias or influence              | 1 | 2 | 3 | 4 | 5 |

## Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity.

Please list any topics you would like to see addressed in future educational activities.

Additional comments about this activity.

## Follow-up

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

- Yes, I would be interested in participating in a follow-up survey.     No, I'm not interested in participating in a follow-up survey.

If you wish to receive acknowledgment for completing for this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876.

## Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

## Request for Credit

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## For Physicians Only:

I certify my actual time spent to complete this educational activity to be: \_\_\_\_\_

- I participated in the entire activity and claim 1.0 credits.  
 I participated in only part of the activity and claim \_\_\_\_\_ credits.