Retreatment with Telaprevir Combination Therapy in Hepatitis C Patients with Well-Characterized Prior Treatment Response

Andrew J. Muir,[1] Fred F. Poordad,[2] John G. McHutchison,[1] Mitchell L. Shiffman,[3] Thomas Berg,[4] Peter Ferenci,[5] E. Jenny Heathcote,[6] Jean-Michel Pawlotsky,[7] Stefan Zeuzem,[8] Henk W. Reesink,[9] Geoffrey Dusheiko,[10] Emily C. Martin,[11] Shelley George,[11] Robert S. Kauffman,[11] and Nathalie Adda[11]

Retreatment with peginterferon alpha and ribavirin (PR) offers a limited chance of sustained virologic response (SVR) in patients who did not achieve SVR with prior PR treatment. This study evaluated the safety and efficacy of telaprevir-based treatment in combination with PR in well-characterized patients who did not achieve SVR in the control arms of three Phase II clinical trials. Patients eligible to enroll in this open-label nonrandomized study either met on-treatment criteria for nonresponse or relapsed after 48 weeks of treatment in the control arm of the three Phase II PROVE studies. The initial protocol was a 24-week regimen: 12 weeks of telaprevir and PR followed by an additional 12 weeks of PR. During the study the protocol was amended to extend PR to 48 weeks for patients with previous null response. All other patients with undetectable hepatitis C virus (HCV) RNA at weeks 4 and 12 received 24 weeks of therapy. Those with detectable HCV RNA at weeks 4 or 12 received a total of 48 weeks of therapy. The overall SVR rate was 59% (69/117). SVR rates with T12PR were 37% (19/51) in prior null responders, 55% (16/29) in prior partial responders, 75% (6/8) in prior breakthroughs, and 97% (28/29) in prior relapsers. The overall relapse rate was 16% (13/83). Adverse events were similar to those in previous trials with telaprevir, with 9% of patients discontinuing due to an adverse event (most commonly rash and anemia). *Conclusion:* This study demonstrated the benefit of retreatment with a telaprevir-based regimen for patients with well-characterized nonresponse (null and partial) or relapse to a prior course of PR treatment. (HEPATOLOGY 2011;00:000-000)

Hepatitis C virus (HCV) infects more than 170 million people worldwide and is the leading cause of cirrhosis and hepatocellular carcinoma in Western countries.[1,2] For the past decade the standard of care treatment regimen for chronic hepatitis C (CHC) has been the combination of peginterferon alpha and ribavirin.[3,4] Although very effective in patients with genotype 2 and 3 infection, peginterferon alpha and ribavirin leads to sustained virologic response (SVR) in 40% to 52% of patients with genotype 1 infection.[5,6] For the many patients who have not responded to peginterferon alpha and ribavirin, options have been limited. Current society guidelines have recommended individualizing decisions on

Abbreviations:: CHC, chronic hepatitis C; eRVR, extended rapid virologic response; HCV, hepatitis C virus; NS3/4A, nonstructural 3/4A HCV protease; SVR, sustained virologic response.

From the [1]Duke Clinical Research Institute and Division of Gastroenterology Duke University Medical Center, Durham, NC; [2]Cedars-Sinai Medical Center, Los Angeles, CA; [3]The Liver Institute of Virginia, Bon Secours Health System, Newport News, VA; [4]University Clinic, Leipzig, Leipzig, Germany; [5]University of Vienna, Vienna, Austria; [6]University of Toronto, Toronto, Ontario, Canada; [7]National Reference Center for Viral Hepatitis B, C and Delta, Department of Virology, Hôpital Henri Mondor, Université Paris-Est, and INSERM U955, Créteil, France; [8]Johann Wolfgang Goethe University Medical Center, Frankfurt am Main, Germany; [9]Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [10]Royal Free and University College School of Medicine, London, United Kingdom; and [11]Vertex Pharmaceuticals Inc., Cambridge, MA.

Received March 17, 2011; accepted June 27, 2011.

Funded by Vertex Pharmaceuticals Inc. and by Tibotec, a division of Janssen-Cilag Ltd. The study sponsors were involved in the trial design and conduct, data collection, and data analysis. Several authors are employees of Vertex Pharmaceuticals Inc.

Address reprint requests to: Andrew J. Muir, M.D., M.H.S., Director, Gastroenterology/Hepatology Research, Duke Clinical Research Institute, P.O. Box 17969, Durham, NC 27715. Express deliveries: 2400 Pratt St., Terrace Level, Room 0311, Durham NC 27701. E-mail: muir0002@mc.duke.edu; Fax: 919-668-7164..

retreatment but have not supported broad retreatment due to the low likelihood of response in nonresponders and the high rate of additional relapse in prior relapsers.[3,4,7] The deficiencies in the current therapeutic regimen have led to the pursuit of alternative drug targets working through different mechanisms of action. Telaprevir is an inhibitor of the nonstructural 3/4A (NS3/4A) HCV protease. In various clinical trials this drug has demonstrated increased SVR rates when given in combination with peginterferon alpha and ribavirin in treatment-naïve and previously treated patients, as compared with peginterferon alpha and ribavirin.[8-10] The present study was initially designed as a rollover protocol to offer telaprevir to the patients in the control arms of the previous Phase II telaprevir studies for those who had not achieved SVR. This approach offered the opportunity to further characterize the safety and efficacy of telaprevir in combination with peginterferon alpha-2a and ribavirin among genotype 1 patients who failed to achieve SVR with prior treatment. An earlier reported Phase II study of telaprevir in previously treated patients relied on historical records to define the prior response.[10] In contrast, by enrolling patients from the control groups of recent clinical trials within the telaprevir program, the present study provided the opportunity to evaluate the efficacy of retreatment with a telaprevir-based regimen in patients with well-characterized interferon responsiveness to prior treatment.

Patients and Methods

Trial Design. The study was initially designed to provide access to telaprevir to patients who did not achieve SVR in the control arms (placebo plus peginterferon alpha-2a and ribavirin) of the Phase II studies of telaprevir combination therapy.[8-10] This open-label, nonrandomized study in patients with chronic genotype 1 HCV infection evaluated the outcomes of treatment with telaprevir-based regimen in these patients with well-characterized prior response to peginterferon alpha-2a and ribavirin. Comparisons between groups defined by prior response or between 24- and 48-week regimens were not study objectives.

Patients. In this rollover study, patients were enrolled at 28 sites in the United States, Puerto Rico, Canada, France, Germany, Austria, and the United Kingdom. Patients from three Phase II parent studies (PROVE1, PROVE 2, and PROVE3)[8-10] with genotype 1 hepatitis C infection were enrolled, but patients with decompensated liver disease and coinfection with hepatitis B or human immunodeficiency virus were excluded. The parent studies evaluated the safety and efficacy of telaprevir in combination with peginterferon alpha-2a and ribavirin in treatment-naïve patients (PROVE 1 and PROVE2) or in patients who had not achieved SVR with prior peginterferon and ribavirin treatment (PROVE3).

Patients were categorized according to previous treatment response to peginterferon alpha-2a and ribavirin as prior null response (less than a 1 $\log_{10}$ decrease in HCV RNA at week 4 or less than a 2 $\log_{10}$ decrease in HCV RNA at week 12 in parent study); prior partial response (greater than a 2 $\log_{10}$ decrease in HCV RNA at week 12 but detectable HCV RNA at week 24 in parent study); prior viral breakthrough (detectable HCV RNA after achieving undetectable HCV RNA during treatment in parent study); and prior relapse (undetectable HCV RNA at end of treatment but detectable HCV RNA within 24 weeks of stopping treatment in parent study).

Eligible patients also had to have an absolute neutrophil count of at least 1,500 per cubic milliliter, platelet count of at least 90,000 per cubic milliliter, and normal hemoglobin.

Interventions. All patients received telaprevir (Vertex Pharmaceuticals, Cambridge, MA) in combination

View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep.24549

Potential conflicts of interest: Dr. Muir currently serves as a consultant/advisor to Vertex, Bristol Myers-Squibb, Merck, Pharmasset, Santaris, and Zymogenetics. He received grant funding from Vertex, Anadys, Gilead, GlaxoSmithKline, Idera, Medtronic, Merck, Pfizer, Pharmasset, Santaris, Three Rivers, and Zymogenetics. Dr. Poordad is a consultant/advisor to Abbott, Achillion, Genentech, Gilead, Idenix, Merck/Schering-Plough, Tibotec, Valeant, and Vertex Pharmaceuticals, and is on the speaker's bureau of Genentech, and Gilead. Dr. Shiffman has received consulting and lecture fees from Abbott, Anadys, Biolex, Bristol Myers-Squibb, Celera Diagnostics, Conatus, Gilead Sciences, Human Genome Sciences, Merck/Schering-Plough, Novartis, Pfizer, Roche/Genentech, Romark, Valeant, Vertex Pharmaceuticals and Zymogenetics; and Grant/Research Support from Biolex, Conatus, Gilead Sciences, GlaxoSmithKline, GlobeImmune, Human Genome Sciences, Idenix, Merck/Schering-Plough, Roche/Genentech, Romark, Tibotec, Valeant, Vertex Pharmaceuticals, Wyeth, and Zymogenetics. Dr. Berg has received consulting and lecture fees from Abbott, Bayer, Gilead Sciences, Merck/Schering-Plough, Novartis, Roche/Genentech, Tibotec and Vertex Pharmaceuticals. Dr. Ferenci has received consulting fees from Boehringer Ingelheim, RottaPharm-Madaus, Roche/Genentech, Tibotec and Vertex Pharmaceuticals; and Grant/Research Support from Roche/Genentech. Dr. Heathcote has received consulting and lecture fees from Axcan Pharma, Gilead Sciences, Hoffman-La-Roche, Merck/Schering-Plough and Tibotec, and Grant/Research Support Axcan Pharma, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Hoffman-La-Roche, Intercept Pharma, Merck/Schering-Plough, Tibotec and Vertex Pharmaceuticals.

with peginterferon alpha-2a 40 kD (Pegasys, Roche, Nutley, NJ) and ribavirin (Copegus, Roche) for 12 weeks, followed by peginterferon alpha-2a and ribavirin. Telaprevir was administered at a dose of 750 mg every 8 hours. Peginterferon alpha-2a was administered at a dose of 180 μg each week subcutaneously. Ribavirin was administered twice daily at a dose of 1,000 mg/day for patients weighing less than 75 kg and a dose of 1,200 mg/day for patients weighing 75 kg or more. Growth factors including erythropoiesis-stimulating agents were prohibited during the course of the study.

In the initial study design, patients received a 24-week regimen with 12 weeks of peginterferon alpha-2a, ribavirin, and telaprevir followed by 12 more weeks of peginterferon alpha and ribavirin. Results from the Phase II prior nonresponder study[10] and preliminary findings from this study led to an amendment in the peginterferon alpha and ribavirin treatment duration according to prior treatment response. In the amended protocol, patients with prior null response to peginterferon alpha-2a and ribavirin would receive 12 weeks of triple combination therapy with peginterferon alpha 2a, ribavirin, and telaprevir followed by 36 more weeks of peginterferon alpha-2a and ribavirin. For patients who experienced prior partial response, viral breakthrough, or relapse the duration of their treatment regimen was determined by their viral response during the first 12 weeks of triple combination therapy with telaprevir. If patients from these groups achieved extended rapid virologic response (eRVR, defined as undetectable HCV RNA at weeks 4 and 12) with the triple combination, they would complete a 24-week course with 12 more weeks of peginterferon alpha-2a and ribavirin alone. If patients from these groups did not achieve eRVR with the triple combination, they would complete a 48-week course with 36 more weeks of peginterferon alpha-2a and ribavirin. Prior to the protocol amendment, 18 prior null responder patients completed just 24 weeks of therapy; six patients gave their consent to the amended protocol but declined treatment extension or did not receive 48 weeks of treatment; and the 27 remaining prior null responder patients were treated under the extended treatment protocol.

Outcomes. Patients were assessed weekly during the first 4 weeks of treatment and then every 4 weeks until the end of the 24- or 48-week treatment course. Following the completion of therapy, patients were evaluated 14 days after the last dose of medication and then at weeks 4, 12, 24, and 48. Safety assessments were conducted through monitoring of adverse events, physical examinations, and review of hematologic and serum chemistry laboratory measurements. Plasma HCV RNA levels were measured at each study visit using the COBAS TaqMan HCV test, v. 2.0 (lower limit of quantitation 25 IU/mL). Stopping rules were developed to discontinue patients in the event of viral breakthrough and to prevent the continuation of treatment in patients who were unlikely to have a response to continued therapy. Viral breakthrough was defined as an increase in HCV RNA of greater than 1 $\log_{10}$ compared with the nadir value or HCV RNA $>$100 IU/mL in a patient who was previously undetectable. The stopping rules were altered during the study based on ongoing review of the Phase II studies.[8,9] The initial stopping rules specified that patients would discontinue if week 4 plasma HCV RNA was greater than 25 IU/mL, or if the reduction in week 12 HCV RNA was less than 2 $\log_{10}$ compared to baseline. In the amended protocol, patients would discontinue if plasma HCV RNA was greater than 100 IU/mL at week 4. Patients with HCV RNA values between 25 and 100 IU/mL had repeat testing within 4 weeks and would discontinue if the repeat HCV RNA value was greater than 100 IU/mL. Patients would also discontinue treatment at week 12 if plasma HCV RNA was greater than 25 IU/mL or if less than 25 IU/mL but detectable by limit of detection.

The study sponsor, Vertex Pharmaceuticals, and the principal investigators were jointly responsible for study design, protocol development, study

Dr. Pawlotsky has received consulting fees from Abbott, Anadys, Biotica, Boehringer-Ingelheim, Bristol-Myers Squibb, DebioPharm, Gilead Sciences, GlaxoSmithKline, Idenix, Janssen-Cilag, Madaus-Rottapharm, Merck/Schering-Plough, Novartis, Pfizer, Roche/Genentech, Tibotec Pharmaceuticals, Valeant Pharmaceuticals, and Vertex Pharmaceuticals; and Grant/Research Support from Gilead Sciences and Roche/Genentech. Dr. Zeuzem has received consulting and lecture fees from Abbott, Achillion, Anadys, Bayer, Bristol-Myers Squibb, Gilead Sciences, Human Genome Sciences, Merck/Schering-Plough, Novartis, Pharmasset, Roche/Genentech, Santaris, Tibotec and Vertex Pharmaceuticals. Dr. Reesink served as an advisor for Anadys, Arrows, Chiron, Gilead Sciences, PRA-International, Merck/Schering-Plough, Novartis, Roche Molecular Diagnostics, Roche/Genentech, Tibotec and Astex, and received Grant/Research support from Merck/Schering-Plough, PRA International, Roche/Genentech and has served as a consultant for Vertex Pharmaceuticals. Dr. Dusheiko has received consulting fees from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Human Genome Sciences, Merck/Schering-Plough, Novartis, Pharmasset, Pfizer, Roche/Genentech, Tibotec, Vertex Pharmaceuticals, and Zymogenetics, travel support from Gilead Sciences, and grant support from, Gilead Sciences, Merck/Schering-Plough, Novartis, Pharmasset, Roche/Genentech, Tibotec and Vertex Pharmaceuticals. Drs Adda, Martin, George and Kauffman are current employees and stock holders of Vertex Pharmaceuticals. Dr. McHutchison is a current employee of Gilead Sciences; has participated in Advisory Committees or review panels for Abbott, Anadys, Biolex, Gilead Sciences, National Genetics Institute, Pharmasset, Pfizer, United Therapeutics; and received Grant/Research Support from GlaxoSmithKline, Globe Immune, Human Genome Sciences, Idera, Intarcia, Medtronics, Merck/Schering Plough, Novartis, Roche/Genentech, Vertex, and Osiris Therapeutics.

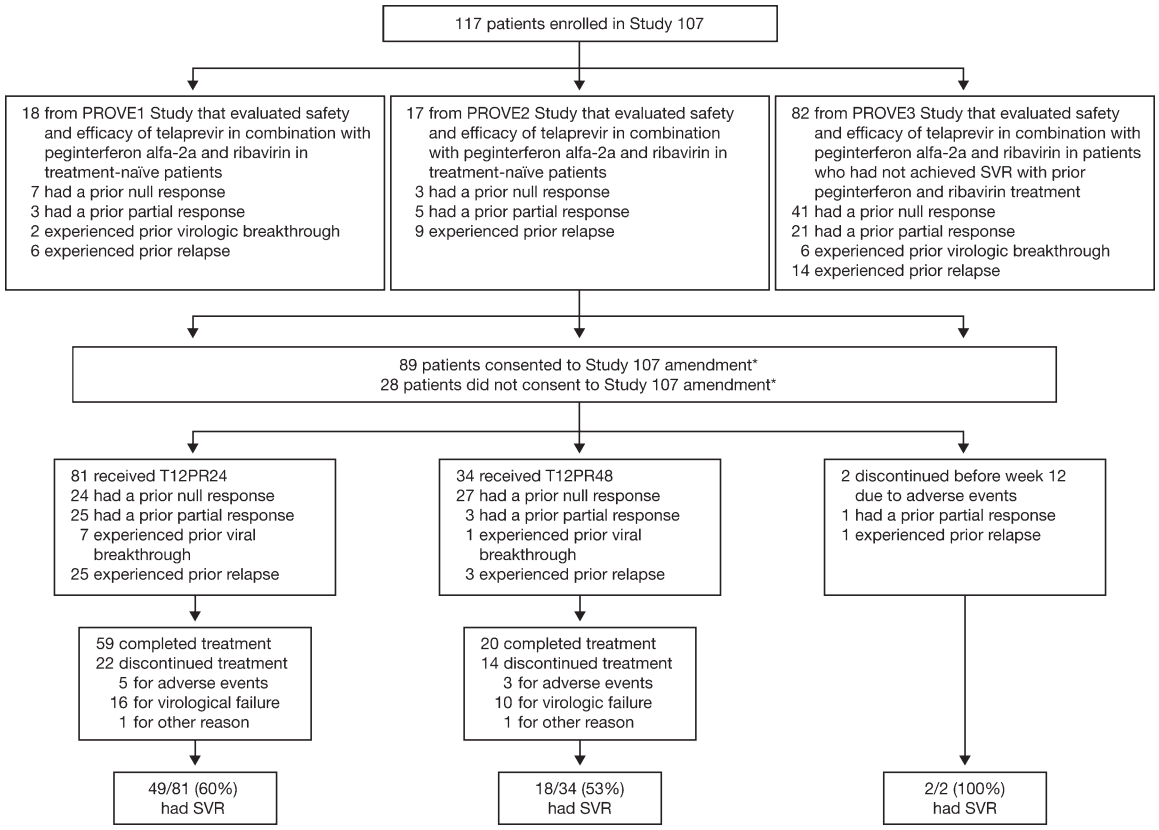

Fig. 1. Disposition and SVR among study patients; 117 patients were enrolled and received at least one dose of study drugs. *Patients with prior null response to peginterferon alpha-2a and ribavirin would receive 12 weeks of triple combination therapy with peginterferon alpha-2a, ribavirin, and telaprevir followed by 36 more weeks of peginterferon alpha-2a and ribavirin. For patients who experienced prior partial response, viral breakthrough or relapse, the duration of their treatment regimen was determined by their viral response during the first 12 weeks of triple combination therapy with telaprevir. If patients from these groups achieved eRVR (defined as undetectable HCV RNA at weeks 4 and 12) with the triple combination, they would complete a 24-week course with 12 more weeks of peginterferon alpha-2a and ribavirin alone. If patients from these groups did not achieve eRVR with the triple combination, they would complete a 48-week course with 36 more weeks of peginterferon alpha-2a and ribavirin.

coordination, and drafting and review of the article. A study publication committee, consisting of a majority of academic authors, agreed on a plan to submit the article for publication. Authors had access to the data, participated in the analysis, and contributed to the writing of the article. The protocol was approved by the regulatory authorities for all participating countries and the Institutional Review Boards for all study centers. The study was performed according to Good Clinical Practice Guidelines. All patients provided written informed consent before study participation.

Statistical Analysis. No formal sample size calculation was performed for this study given the initial goal to provide access to telaprevir for patients in the control arms of the original studies in which they had participated. The analysis included data for all patients who received at least one dose of study drugs. The primary endpoint was the proportion of patients with undetectable plasma HCV RNA 24 weeks after the completion of treatment (SVR). Although the protocol was amended to provide extended duration of treatment, the protocol was not designed to compare outcomes in the groups with different durations of treatment. All statistical analyses were performed using the validated v. 9.1.3 of the SAS System (SAS Institute, Cary, NC).

Results

Patient Characteristics. Between October 2007 and November 2008, 117 patients were enrolled and received at least one dose of the study drug regimen as outlined in Fig. 1. Of the 117 patients, 35 (30%) had been previously enrolled in the Phase II treatment-naïve PROVE1 and PROVE2 trials, and 82 (70%) had been enrolled in the Phase II trial of treatment-experienced patients PROVE3. Most of the patients in this study therefore had previously received at least two courses of treatment. The mean time elapsed between the end of the prior treatment course in the parent

Table 1. Baseline Characteristics According to Prior Treatment Response

	Previous Response					
Variable	Null Response T12PR24 n = 24	Null Response T12PR48 n = 27	Partial Response n = 29	Viral Breakthrough n = 8	Relapse n = 29	Total N = 117
Age, mean (years) (range)	49 (19-60)	51 (34-63)	51 (27-62)	50 (46-55)	50 (31-60)	50 (19-63)
BMI, mean kg/m^2 (range)	30 (21-57)	30 (21-41)	28 (20-37)	25 (18-28)	26 (19-39)	28 (18-57)
Sex male, n (%)	14 (58)	23 (85)	22 (76)	4 (50)	18 (62)	81 (69)
Race, n (%)						
White	22 (92)	24 (89)	27 (93)	7 (88)	26 (90)	106 (91)
Black	2 (8)	3 (11)	1 (3)	1 (12)	2 (7)	9 (8)
Other	0 (0)	0 (0)	1 (3)	0 (0)	1 (3)	2 (2)
Ethnicity, n (%)						
Hispanic/Latino	2 (8)	2 (7)	3 (10)	0 (0)	2 (7)	9 (8)
Not Hispanic/Latino	22 (92)	25 (93)	26 (90)	8 (100)	27 (93)	108 (92)
Geographic region, n (%)						
Europe	1 (4)	7 (26)	6 (21)	0 (0)	11 (38)	25 (21)
North America	23 (96)	20 (74)	23 (79)	8 (100)	18 (62)	92 (79)
HCV genotype 1 subtype, n (%)						
1a	14 (58)	16 (59)	17 (59)	5 (62)	17 (59)	69 (59)
1b	8 (33)	10 (37)	7 (24)	3 (38)	10 (34)	38 (32)
1, unknown	2 (8)	1 (4)	5 (17)		2 (7)	10 (9)
HCV RNA ≥800,000 IU/mL	23 (96)	27 (100)	25 (86)	3 (38)	19 (66)	97 (83)
Stage of fibrosis, n (%)						
None or minimal fibrosis	5 (21)	6 (22)	8 (28)	2 (25)	8 (28)	29 (25)
Portal fibrosis	8 (33)	10 (37)	9 (31)	2 (25)	15 (52)	44 (38)
Bridging fibrosis	9 (38)	9 (33)	7 (24)	4 (50)	5 (17)	34 (29)
Cirrhosis	2 (8)	2 (7)	5 (17)	0 (0)	1 (3)	10 (9)

study and enrollment in the current protocol was 7 months with a range from 1 to 17 months. No specified washout period was required.

Baseline characteristics of the patients are detailed in Table 1, according to prior treatment response. Of the patients with prior null response, the majority (21/24 patients in the 24-week treatment arm and 24/27 patients in the 48-week treatment arm) had less than a 1 $\log_{10}$ decrease in HCV RNA at week 4 in their prior course of treatment. The remaining six patients had greater than a 1 $\log_{10}$ decrease in HCV RNA at week 4 but less than a 2 $\log_{10}$ decrease in HCV RNA at week 12 in their parent study. The protocol amendment that altered treatment duration had the greatest impact on patients with null response so these patients are listed according to the 24- or 48-week treatment course. Most patients were male (69%) and Caucasian (91%) with HCV RNA ≥800,000 IU/mL at baseline (83%) and genotype 1a infection (59%). More than a third of the patients had bridging fibrosis (29%) or cirrhosis (9%).

Patient Disposition. Figure 1 describes the patient disposition throughout the study. Treatment duration was altered during the study based on findings from ongoing studies with telaprevir.[8,9] In the initial preamendment phase of enrollment, all patients received the 24-week regimen regardless of prior treatment response. In the latter postamendment phase, prior null responders and other patients not achieving eRVR received the 48-week regimen. In addition, nine patients (six prior null responders, one prior partial responder, and two prior relapsers) consented to the amendment, but declined treatment extension or did not receive 48 weeks of treatment. As a result, there were 24 patients with prior null response who received the 24-week regimen. Two patients (one prior partial responder and one prior relapser) discontinued treatment prior to week 12 due to adverse events and therefore were not assessed for eRVR status or assigned to a 24- or 48-week treatment regimen.

A total of 79 patients (68%) completed treatment and 38 (32%) discontinued treatment prematurely. The most frequent reasons for premature treatment discontinuation were protocol-defined stopping rules (26 [22%]) and adverse events (10 [9%]).

Efficacy Outcomes. Table 2 reports the rates of undetectable HCV RNA levels during and after treatment, according to the prior treatment response and by baseline predictor variables. The overall rate for the primary endpoint of SVR was 59% (69/117). The SVR rate was highest among patients who previously relapsed (97%), followed by the prior viral breakthrough patients (75%), and prior partial response patients (55%). Among prior null responders the

Table 2. Efficacy Outcomes During and After the Treatment Period, According to Prior Treatment Response and According to Baseline Predictor Variables

	Previous Response					
Efficacy Outcome, n/N (%)	Null response T12PR24 n = 24	Null response T12PR48 n = 27	Partial response n = 29	Viral breakthrough n = 8	Relapse >n = 29	Total N = 117
	Number/total number (percent)					
HCV RNA undetectable during treatment period						
Week 2	0/24 (0)	2/27 (7)	8/29 (28)	4/4 (50)	14/29 (48)	28/117 (24)
Week 4	5/24 (21)	16/27 (59)	25/29 (86)	7/8 (88)	27/29 (93)	80/117 (68)
Week 12	7/24 (29)	23/27 (85)	24/29 (83)	6/8 (75)	26/29 (90)	86/117 (74)
End of treatment	6/24 (25)	19/27 (70)	23/29 (79)	6/8 (75)	29/29 (100)	83/117 (71)
Sustained virologic response						
All patients	4/24 (17)	15/27 (56)	16/29 (55)	6/8 (75)	28/29 (97)	69/117 (59)
By race						
White	4/22 (18)	13/24 (54)	15/27 (56)	5/7 (71)	25/26 (96)	62/106 (58)
Black	0/2 (0)	2/3 (67)	0/1 (0)	1/1 (100)	2/2 (100)	5/9 (56)
By ethnicity						
Hispanic/Latino	0/2 (0)	1/2 (50)	2/3 (67)	NA	2/2 (100)	5/9 (56)
Not Hispanic/Latino	4/22 (18)	14/25 (56)	14/26 (54)	6/8 (75)	26/27 (100)	64/108 (59)
By HCV genotype 1 subtype						
1a	2/14 (14)	9.16 (56)	8/17 (41)	5/5 (100)	17/17 (100)	41/69 (59)
1b	1/8 (12)	6/10 (60)	5/7 (71)	1/3 (33)	9/10 (90)	22/38 (58)
By HCV RNA levels						
HCV RNA ≥800,000 IU/mL	4/23 (17)	15/27 (56)	13/25 (52)	1/3 (33)	18/19 (95)	51/97 (53)
HCV RNA <800,000 IU/mL	0/1 (0)	NA	3/4 (75)	5/5 (100)	10/10 (100)	18/20 (90)
By stage of fibrosis (%)						
None or minimal fibrosis	1/5 (20)	0/6 (0)	7/8 (88)	2/2 (100)	8/8 (100)	18/29 (62)
Portal fibrosis	3/8 (38)	8/10 (80)	4/9 (44)	1/2 (50)	14/15 (93)	30/44 (68)
Bridging fibrosis	0/9 (0)	6/9 (67)	3/7 (43)	3/4 (75)	5/5 (100)	17/34 (50)
Cirrhosis	0/2 (0)	1/2 (50)	2/5 (40)	NA	1/1 (100)	4/10 (40)
Relapse						
All patients	2/6 (33)	4/19 (21)	6/23 (26)	0/6 (0)	1/29 (3)	13/83 (16)
Patients who completed treatment	1/5 (20)	3/16 (19)	5/21 (24)	0/6 (0)	0/26 (0)	9/74 (12)
Patients who stopped treatment prematurely	1/1 (100)	1/3 (33)	1/2 (50)	NA	1/3 (33)	4/9 (44)

overall SVR rate was 37% (19/51) with 56% (15 of 27 patients) in the 48-week treatment group and 17% (4 of 24 patients) in the 24-week treatment group. This difference in response was observed as early as 4 weeks of treatment, when 59% were undetectable in the 48-week treatment group compared with 21% in the 24-week treatment group.

Discontinuations due to the week 4 stopping rule were more frequent in patients assigned to the 24-week regimen (eight patients, 10%) than in those assigned to the 48-week regimen (one patient, 3%). As previously mentioned, the week 4 stopping rule was amended during the course of the study following review of data from the Phase II studies.[8,9] The original week 4 stopping rule called for patients to discontinue treatment if the week 4 plasma HCV RNA level was >25 IU/mL, whereas the amended rule called for discontinuation if the week 4 plasma HCV RNA level was >100 IU/mL. Treatment was also discontinued if the level was between 25-100 IU/mL upon initial testing and >100 IU/mL upon repeat testing within 4 weeks. To assess whether the higher frequency of discontinuations in patients who received the 24-week regimen compared to patients who received the 48-week regimen was attributable to the above changes in week 4 stopping rules, an analysis was conducted to determine the number of subjects in each treatment group who had their week 4 stopping rule assessed prior and after rule change. All eight patients in the 24-week group who discontinued treatment due to their week 4 HCV RNA levels had levels ≥25 IU/mL and six of the eight patients had levels >100 IU/mL at week 4 or had levels <100 IU/mL but had a confirmatory values of at least 100 IU/mL. The difference was therefore not attributable to the changes in the week 4 stopping rules during the study.

The SVR rates are reported for patients in each group according to known predictors of response including baseline viral load genotype 1a and 1b, fibrosis, and others as shown. Most patients experiencing relapse were prior null and partial responders. Relapse at or before week 24 of follow-up did not

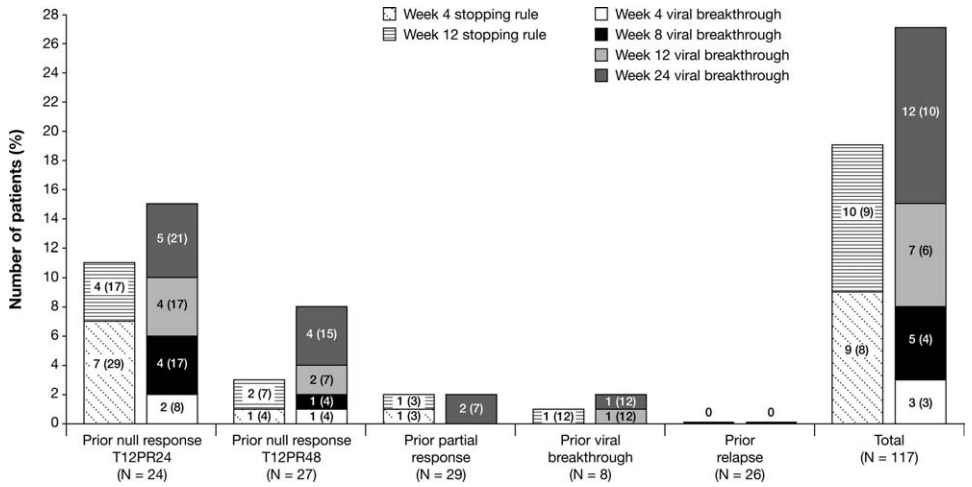

Fig. 2. Virologic failure on treatment. Bars represent the number (percentage) of patients in the different treatment groups who experienced virologic failure on treatment.

occur in the patients with prior viral breakthrough and occurred in only one patient with prior relapse. Of the 64 patients who completed the full course of treatment and achieved SVR at follow-up week 24 (so-called completers), 63 returned for assessment and all demonstrated durable SVR. On-treatment virologic failure is depicted in Fig. 2. In summary, 11 of the 15 cases of viral breakthrough occurred in patients with previous null response, and seven of the 15 occurred during the first 12 weeks of retreatment that included telaprevir.

Safety. Adverse events reported in more than 10% of the patients are reported in Table 3. The safety profile was similar to that observed in the earlier Phase II studies. Rash and pruritus have been more common in patients treated with telaprevir in previous trials and these were again observed. Rash occurred in 32 (27%) patients during the first 12 weeks of treatment, which included telaprevir, and in five additional patients during the latter phase with peginterferon alpha-2a and ribavirin. Using a variety of descriptive terms to identify all dermatologic events, rash events occurred in 50 (43%) of patients during the telaprevir phase and in six additional patients in the latter phase. Severe rash events were reported in six (5%) patients; all of these events occurred during the first 12 weeks of treatment and resolved after treatment discontinuation. Pruritus occurred in 41 (35%) patients during the telaprevir treatment phase and four additional patients after the telaprevir treatment phase during treatment with peginterferon alpha-2a and ribavirin alone. Changes in laboratory values during the study were generally consistent with those reported in association with peginterferon alpha-2a and ribavirin. Decreases in hemoglobin levels, increases in uric acid levels, and increases in total bilirubin levels were more common during the telaprevir treatment phase.

Adverse events led to discontinuation of all study drugs in 10 (9%) patients and eight (7%) patients during the telaprevir treatment phase. The adverse events leading to discontinuation in two or more patients were rash events (six) including pruritus (two), anemia (two), and pyrexia (two). One rash event was reported as drug rash with eosinophilia and systemic symptoms (DRESS) with onset at day 56 of treatment and leading to hospitalization for 1 week. Study medications were discontinued and the patient fully recovered but did not achieve SVR. Other adverse events reported in one patient who permanently discontinued treatment were urticaria, lymphadenopathy, pancytopenia, asthenia, face edema, injection-site rash, peripheral edema, pain, infectious bursitis, dehydration, hypokalemia, costochondritis, headache, pleurisy, and hypotension. Two patients had adverse events leading to discontinuation of all study drugs during treatment with peginterferon alpha-2a and ribavirin alone and the adverse events reported were fatigue, rhabdomyolysis, and depression.

Discussion

In this study, retreatment with a telaprevir-based regimen in carefully characterized patients who have previously failed treatment with peginterferon alpha and ribavirin in the setting of a controlled clinical trial yielded higher SVR rates than historically observed with peginterferon and ribavirin. This trial provided the unique opportunity for patients to receive treatment from the same providers with the same doses of

Table 3. Adverse Events Leading to Discontinuation and Most Common Adverse Events Reported According to Treatment Group

n (%)	T12PR24 N = 81	T12PR48 N = 34	Unassigned* N = 2	Total N = 117
Adverse events leading to discontinuation†	5 (6)	3 (9)	2 (100)	10 (9)
Rash events‡	4 (5)	1 (3)	1 (50)	6 (5)
Pruritus	1 (1)	0 (0)	1 (50)	2 (2)
Pyrexia	1 (1)	1 (3)	0 (0)	2 (2)
Anemia	2 (2)	0 (0)	0 (0)	2 (2)
Adverse events occurring in >10% of patients, n (%)				
Severe adverse event	12 (15)	7 (21)	1 (50)	20 (17)
General disorder				
Fatigue	30 (37)	21 (62)	1 (50)	52 (44)
Influenza-like illness	17 (21)	10 (29)	1 (50)	28 (24)
Pyrexia	16 (20)	6 (18)	0 (0)	22 (19)
Chills	11 (14)	4 (12)	0 (0)	15 (13)
Asthenia	9 (11)	3 (9)	0 (0)	12 (10)
Gastrointestinal disorder				
Nausea	20 (25)	11 (32)	1 (50)	32 (27)
Diarrhea	19 (24)	6 (18)	0 (0)	25 (21)
Hemorrhoids	9 (11)	4 (12)	0 (0)	13 (11)
Skin and subcutaneous disorders				
Pruritus	34 (42)	9 (26)	2 (100)	45 (38)
Rash§	23 (28)	13 (38)	1 (50)	37 (32)
Dry skin	10 (12)	5 (15)	0 (0)	15 (13)
Nervous system disorders				
Headache	23 (28)	14 (41)	0 (0)	37 (32)
Psychiatric disorders				
Insomnia	14 (17)	7 (21)	1 (50)	22 (19)
Depression	9 (11)	4 (12)	0 (0)	13 (11)
Musculoskeletal disorders				
Myalgia	10 (12)	5 (15)	0 (0)	15 (13)
Arthralgia	11 (14)	2 (6)	0 (0)	13 (11)
Respiratory disorders				
Cough	9 (11)	4 (12)	2 (100)	15 (13)
Blood and lymphatic disorders				
Anemia	22 (27)	7 (21)	0 (0)	29 (25)

*Unassigned patients discontinued treatment prior to week 12 assignment of treatment duration.

†Adverse events leading to discontinuation in ≥2 patients.

‡This category includes all patients experiencing rash events as assessed with the use of a group of related terms to identify all dermatologic events. All treatment discontinuations due to rash happened during telaprevir phase.

§Using a variety of descriptive terms to identify all dermatologic events, rash events occurred in 44%, 53%, 100%, and 48% of T12PR24, T12PR48, Unassigned, and Total patients, respectively.

peginterferon alpha-2a and ribavirin with only one major change, the addition of telaprevir to their treatment regimen.

In other respects, the findings were similar to the previously reported Phase II studies with telaprevir. Discontinuation due to an adverse event occurred in 9% of patients in the study and the most common reason for discontinuation was rash. The efficacy results are similar to those in the recently reported Phase II study of telaprevir in previously treated patients, but one advantage was that these patients were well-characterized due to their prior enrollment in trials in the telaprevir program.[8-10] In the recent Phase II retreatment study, the response rate for prior nonresponders was 38% to 39% in the treatment arms with telaprevir.[10] In this study, nonresponder patient SVR rates are reported with more detailed categorization as prior null responders (37%), prior partial responders (55%), and prior breakthrough (75%). The SVR rate for prior relapsers was 97% with just one patient experiencing relapse again. Relapse occurred in 16% of patients in whom HCV RNA was undetectable at the end of treatment, and 12 of the 13 cases occurred in prior null responders or prior partial responders. Similarly, 11 of the 15 cases of viral breakthrough occurred in patients with prior null response. This detailed understanding of the previous virologic response could help guide clinicians when thinking about a patient's prior response pattern and determining the potential benefit from retreatment with a telaprevir regimen.

Within each prior treatment group, we also reported response rates according to racial group and degree of fibrosis, but the results should be interpreted with caution given the small sample sizes. However, each subgroup demonstrated encouraging response rates compared with historical controls of retreatment with standard of care with the exception of the prior null responders in the 24-week treatment arm.[10]

Because of ongoing findings from a number of studies with telaprevir, the approach to treatment duration was altered during this study.[8,9] Most patients completed the original planned 24 weeks of treatment. The main impact of this amendment was on the prior null responder group, where 53% completed 48 weeks of treatment. The 48-week treatment group SVR was 56%, whereas the 24-week treatment group SVR was 17%, but statistical comparisons cannot be made between these groups as this was not a prospective plan with randomization. Interestingly, this difference in treatment response was observed already at week 4 of treatment when the patients were receiving the same regimen. We therefore cannot conclude that treatment duration was a key contributor to this observed difference. In examining the baseline characteristics of these prior null response patients, no obvious factor explains these varied responses among the two treatment groups.

In conclusion, this study demonstrated the benefit of retreatment with a telaprevir-based regimen for a broad range of well-characterized patients who previously failed HCV treatment including prior null responders. Adverse events were similar to those in previous trials with telaprevir, with 9% of patients discontinuing due to an adverse event (most commonly rash, pruritus, and anemia).

Acknowledgment: We thank the following investigators for their contribution to the study: Canada: Mang Ma, Robert Myers, Morris Sherman, Eric Yoshida; France: Patrice Couzigou, Stanislas Pol, Lawrence Serfaty, Albert Tran, Christian Trépo, Germany: Peter Buggish, Andreas Erhardt, Tobias Goeser, Michael Manns, Ulrich Spengler; The Netherlands: Rob de Knegt; United States: Nezam Afdhal, Sanjeev Arora, David Bernstein, Robert Brown, Joseph Cochran, Adrian Di Bisceglie, Rolland Dickson, Douglas Dieterich, Kyle Etzkorn, Greg Everson, Shaban Faruqui, Reem Ghalib, Norman Gitlin, Stuart Gordon, Tarek Hassanein, Ira Jacobson, Alan Kilby, Marcello Kugelmas, Eric Lawitz, Karen Lindsay, David Nelson, Patrick Northup, Lisa Nyberg, Keyur Patel, Maribel Rodriguez-Torres, Obaid Shaikh, Eugene Schiff, Kenneth Sherman, Jill Smith, James Strohecker, Mark Sulkowski, Gyongi Szabo, Helen Te, Norah Terrault, John Vierling, Lawrence Wruble, Zobair Younossi. We thank the study coordinators, nurses, and patients involved in the study; Desiree Devonish (Vertex Pharmaceuticals Inc.) for clinical project management; John Alam, M.D. (a former employee of Vertex Pharmaceuticals Inc.) for contribution to the design of the study; Doug Bartels, Ph.D. and Tara Kieffer, Ph.D. for virology analysis; Eric Stevenson, Ph.D. for data accuracy and Valérie Philippon, Ph.D., for editorial assistance and coordination support (all from Vertex Pharmaceuticals Inc.).

References

1. Di Bisceglie AM, Lyra AC, Schwartz M, Reddy RK, Martin P, Gores G, et al. Hepatitis C-related hepatocellular carcinoma in the United States: influence of ethnic status. Am J Gastroenterol 2003;98:2060-2063.
2. Global surveillance and control of hepatitis C: report of a WHO Consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. J Viral Hepat 1999;6:35-47.
3. Dienstag JL, McHutchison JG. American Gastroenterological Association Medical Position Statement on the Management of Hepatitis C. Gastroenterology 2006;130:225-230.
4. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. HEPATOLOGY 2009;49: 1335-1374.
5. Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004;140:346-355.
6. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 2009;361:580-593.
7. Poynard T, Colombo M, Bruix J, Schiff E, Terg R, Flamm S, et al. Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. Gastroenterology 2009; 136:1618-1628.
8. Hézode C, Forestier N, Dusheiko G, Ferenci P, Pol S, Goeser T, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med 2009;360:1839-1850.
9. McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffman R, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med 2009;360: 1827-1838 [erratum, N Engl J Med 2009;361:1516].
10. McHutchison JG, Manns MP, Muir AJ, Terrault NA, Jacobson IM, Afdhal NH, et al. Telaprevir for previously treated chronic HCV infection. N Engl J Med 2010;362:1292-1303.