SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec BVBA **Trade Name**: - **Indication**: Chronic hepatitis C virus infection	**Drug Substance**: VX-950 (telaprevir) **Trial no**.: VX-950-TiDP24-C208 **Clinical Phase**: IIa
Title: A Phase IIa randomized, open-label study of telaprevir (VX-950) administered every 12 or every 8 hours in combination with either Peg-IFN-alfa-2a (Pegasys®) and ribavirin (Copegus®) or Peg-IFN-alfa-2b (PegIntron®) and ribavirin (Rebetol®) in treatment-naïve subjects with chronic genotype 1 hepatitis C infection	
Coordinating Investigator: [redacted] M.D., Ph.D., Hôpital Beaujon, Service d'Hépatologie, Pavillon Abrami, [redacted] France	**Countries**: Austria, Belgium, France, Germany, Italy, Spain, The Netherlands
Trial Period: Start: 30-Oct-2007 End: 20-Aug-2009 20 August 2009 was the date of database lock. All subjects had either completed or discontinued the trial prematurely by 20 August 2009, except for one subject who still had to attend the visit 24 weeks after relapse. This visit took place on 14 September 2009.	**No. of Investigators**: 30 **No. of Subjects**: 161
Objectives: The objective of the present trial was to explore the efficacy, safety, tolerability, pharmacokinetics, and pharmacokinetic-pharmacodynamic relationships of telaprevir when administered as 750 mg every 8 hours (q8h) or 1125 mg every 12 hours (q12h) in combination with pegylated interferon (Peg-IFN)-alfa-2a (Pegasys®) and ribavirin (RBV; Copegus®) or Peg-IFN-alfa-2b (PegIntron®) and RBV (Rebetol®).	
Design: This was an open-label, randomized, multicenter trial in subjects with chronic genotype 1 hepatitis C virus (HCV) infection who were randomized to receive 1 of 2 different dose regimens of telaprevir in combination with standard therapy (Peg-IFN-alfa-2a [Pegasys®] and RBV [Copegus®] or Peg-IFN-alfa-2b [PegIntron®] and RBV [Rebetol®] at the standard doses). A total of 160 subjects (40 per treatment group) were planned to be enrolled. The trial consisted of a screening phase of approximately 4 weeks, a treatment phase of up to 48 weeks, and a follow-up phase of at least 24 weeks. Subjects were randomized to 1 of 4 treatment groups: T12(q8h)/P(2a)R: telaprevir 750 mg q8h with Pegasys/Copegus T12(q8h)/P(2b)R: telaprevir 750 mg q8h with PegIntron/Rebetol T12(q12h)/P(2a)R: telaprevir 1125 mg q12h with Pegasys/Copegus T12(q12h)/P(2b)R: telaprevir 1125 mg q12h with PegIntron/Rebetol All subjects received 12 weeks of telaprevir treatment in combination with standard therapy (i.e., Peg-IFN and RBV). At Week 12, telaprevir dosing ended and subjects continued on standard therapy only. The total duration of treatment depended on the subjects' individual on-treatment viral response and was maximally 48 weeks: 1. Peg-IFN and RBV treatment was stopped at Week 24 if a subject's HCV RNA was undetectable (i.e., no HCV RNA was detected in the subject's plasma samples) from Week 4 through Week 20. 2. Peg-IFN and RBV treatment was continued up to Week 48 if a subject did not have undetectable HCV RNA at Week 4 (i.e., the subject did not have rapid viral response [RVR]), but the subject's HCV RNA level became undetectable at any visit after Week 4 and remained undetectable until Week 20.	

3. In situations not captured by rules 1 and 2 (i.e., for different patterns of viral response), viral response was analyzed case by case, and the treatment duration of Peg-IFN and RBV was decided by the Virology Monitor.

After the end of treatment (EOT, i.e., having completed treatment or having discontinued all study medication earlier), all subjects were followed-up for at least 24 weeks in order to assess sustained viral response (SVR24) or to collect samples for viral sequencing:

- If at EOT HCV RNA was undetectable, follow-up visits were planned at Follow up Week 4, Week 8, Week 12, Week 24, and Week 26. The purpose of the Follow-up Week 26 visit was to communicate the HCV RNA result from the previous visit to the subject.
- If at EOT the HCV RNA was detectable, follow-up visits were only planned at Follow-up Week 4 and Week 24.

SVR24 was defined as having undetectable HCV RNA at EOT and no confirmed detectable HCV RNA levels between EOT and 24 weeks after the last dose of study medication.

If at any time during the follow-up period a subject experienced a confirmed relapse, the subject did not complete the planned follow-up visit schedule but was asked to attend an additional visit 24 weeks after the relapse instead (i.e., visit 24 weeks after first detectability). Relapse was defined as having confirmed detectable HCV RNA levels during the follow-up period in subjects who had undetectable HCV RNA at the end of treatment.

Extensive virologic assessments and pharmacokinetic evaluations were performed. HCV RNA was measured throughout the treatment period and during the follow-up period. Samples for viral sequencing of the HCV NS3-4A region were analyzed upon request of the protocol virologist. Adherence to the dosing schedule of telaprevir was assessed.

A substudy was performed within the framework of this trial in which full pharmacokinetic profiles were assessed in a subset of 15 subjects per treatment group. In this substudy early viral kinetics were also assessed in the same subset of subjects to determine the effectiveness (epsilon) of the different treatment regimens.

Subject Selection

Inclusion Criteria

1. Male and female subjects 18 to 65 years of age, inclusive.
2. Chronic genotype 1 hepatitis C infection. Chronic disease status had to be confirmed by at least 1 of the following standard criteria:
   - history of a remote risk factor (e.g., intravenous drug abuse or blood transfusion); or
   - abnormal alanine aminotransferase (ALT) levels for > 6 months prior to screening (note: elevated ALT was not an inclusion criterion if one of the other criteria for chronic hepatitis C was met); or
   - diagnosis of hepatitis C > 6 months before the screening period.

   Note: To ensure an equal balance between the genotypes 1a and 1b (based on the 5'NC – Trugene genotyping method), the number of subjects from either subtype was limited to a maximum of 60% of the total number of subjects.
3. Naïve of therapy for HCV (including investigational products).
4. Screening laboratory values of the following variables had to meet the following acceptable values: absolute neutrophil count ≥ 1,500/mm^3, platelet count ≥ 100,000/mm^3, bilirubin within normal range (except for subjects with Gilbert's Syndrome), and hemoglobin within normal range. All other hematology and clinical chemistry results had to show no clinically significant abnormalities, as judged by the investigator.
5. Plasma HCV RNA > 10,000 IU/mL at entry.
6. Liver biopsy (preferred) or Fibroscan (alternative) within three years of the screening visit to assess the degree of liver fibrosis. The reports from either diagnostic procedure were to be documented in the subject's medical chart. If no biopsy or Fibroscan results were available at screening, such procedure had to be performed as part of the screening procedures.
7. Judged to be in good health (apart from HCV infection), in the opinion of the investigator.

8. Female subjects of childbearing potential had to agree to use two effective methods of contraception, if heterosexually active, from screening until 4 months after last dose of RBV.
   Non-vasectomized male subjects who had a female partner of childbearing potential had to agree to use two effective methods of contraception, if heterosexually active, from screening until 7 months after last dose of RBV.
   Note: Hormonal contraceptives may not be reliable when taking telaprevir.
   Therefore, to be eligible for this trial, female subjects were to use 2 barrier methods during telaprevir treatment and the subsequent month. Barrier contraceptives included but were not limited to the following methods: male condom, diaphragm with spermicidal jelly, cervical cap, or female condom (note that the female condom was not to be used simultaneously with a latex male condom because the friction between the two condoms could cause the condoms to break). As of one month after completion of telaprevir treatment, hormonal contraceptives could be used as one of the 2 required efficient methods of birth control.
   Note: The use of birth control methods did not apply if the male partner had undergone a vasectomy or if the female sexual partner had had a bilateral oophorectomy, or a total hysterectomy, or if she was postmenopausal for at least two years.
9. Willing to refrain from the concomitant use of any medications, substances or foods noted in Section 3.3.8.
10. Informed Consent Form (ICF) signed voluntarily before first trial-related activity.
11. Having agreed not to participate in other clinical trials (with the exception of observational trials) for the duration of his/her participation in this trial.

Exclusion Criteria

1. Presence of a concomitant medical condition that in the opinion of the investigator could have influenced the results of the trial or that could have represented an additional risk for the administration of the study medication to the subject.
2. Any medical contraindications to Peg-IFN-alfa-2a, Peg-IFN-alfa-2b, or RBV therapy, including but not limited to the following:
   - abnormal thyroid-stimulating hormone (TSH) levels (except if well-controlled on medication) or poorly controlled thyroid function;
   - evidence of clinically significant cardiac dysfunction;
   - history of psychiatric disorders determined by the investigator contraindicating the use of IFN-based therapy;
   - evidence of autoimmune disease;
   - history of hemoglobinopathies.
3. History or evidence of cirrhosis or decompensated liver disease defined as a prior or current history of ascites, hepatic encephalopathy, bleeding esophageal, or gastric varices.
4. Any evidence of significant liver disease in addition to hepatitis C; this could include but was not limited to, hepatitis B, drug or alcohol-related cirrhosis, autoimmune hepatitis, hemochromatosis, Wilson's disease, nonalcoholic steatohepatitis, or primary biliary cirrhosis.
5. Diagnosed or suspected hepatocellular carcinoma. Alfa-fetoprotein (AFP) at screening had to be less than 50 ng/mL, or if higher, absence of a mass on an ultrasound or magnetic resonance imaging (MRI) scan had to be documented within the screening period.
6. History or suspicion of alcohol, barbiturate, or amphetamine recreational or narcotic drug use, which in the investigator's opinion would have compromised the subject's safety and/or compliance with trial procedures.
7. Human immunodeficiency virus (HIV) or hepatitis B virus (HBV) co-infection.
8. Women who were pregnant, planning on becoming pregnant, or were breastfeeding, and partners of women who were pregnant or breastfeeding.
9. Hypersensitivity to tartrazine.
10. Subject had participated in any clinical trial for an investigational drug within 90 days before drug administration or had participated in more than 2 drug trials in the last 12 months.

Treatment	**Telaprevir**	**Peg-IFN-alfa-2a (Pegasys)**	**Peg-IFN-alfa-2b (PegIntron)**	**RBV (Copegus)**	**RBV (Rebetol)**
Concentration	375 mg	180 µg	50 µg/0.5 mL, 80 µg/0.5 mL, 100 µg/0.5 mL, 120 µg/0.5 mL, 150 µg/0.5 mL	200 mg	200 mg
Dosage Form	tablet	solution	powder and solvent for solution	tablet	capsule
Usage	oral	injection	injection	oral	oral
Batch Number	3057618R 3060433R 3060435R	B1049 B1052 B1059	50 µg/0.5 mL: 6IRA30202, 7IRA60137 80 µg/0.5 mL: 6IRG30318, 6IRG30403, 7IRG60140 100 µg/0.5 mL: 7IRB60301, 6IRB60409 120 µg/0.5 mL: 6IRJ60807, 7IRJ60140 150 µg/0.5 mL: 6IRC60436, 7IRC60213, 7IRC60520	B3085 B3085/2 B3092 B3095 92199	6RCJA43A04 6RCJA47B06 7RCJA21A09
Dose Regimen	Subjects were randomized to 1 of 4 treatment groups: T12(q8h)/P(2a)R: telaprevir 750 mg q8h from Day 1 through Week 12; Peg-IFN-alfa-2a (Pegasys) 180 µg/week and RBV (Copegus) 1,000 - 1,200 mg/day[a] (twice daily regimen) from Day 1 up to Week 48 T12(q8h)/P(2b)R: telaprevir 750 mg q8h from Day 1 through Week 12; Peg-IFN-alfa-2b (PegIntron) 1.5 µg/kg/week and RBV (Rebetol) 800 - 1,200 mg/day[b] (twice daily regimen) from Day 1 up to Week 48 T12(q12h)/P(2a)R: telaprevir 1125 mg q12h from Day 1 through Week 12; Peg-IFN-alfa-2a (Pegasys) 180 µg/week and RBV (Copegus) 1,000 – 1,200 mg/day[a] (twice daily regimen) from Day 1 up to Week 48 T12(q12h)/P(2b)R: telaprevir 1125 mg q12h from Day 1 through Week 12; Peg-IFN-alfa-2b (PegIntron) 1.5 µg/kg/week and RBV (Rebetol) 800 –1,200 mg/day[b] (twice daily regimen) from Day 1 up to Week 48 [a] Copegus dosing was weight-based: < 75 kg = 1,000 mg, ≥ 75 kg = 1,200 mg [b] Rebetol dosing was weight-based: < 65 kg = 800 mg, ≥ 65 and ≤ 85 kg = 1,000 mg, > 85 kg = 1,200 mg				
Duration of Treatment	All subjects received 12 weeks of telaprevir in combination with standard therapy (Peg-IFN and RBV), followed by standard therapy only. The total duration of treatment depended on the subjects' individual on-treatment viral response and was up to 48 weeks (see design section).				
Duration of Trial	Screening: approximately 4 weeks Treatment: up to 48 weeks Follow-up: at least 24 weeks				
Disallowed Medication	Because of the interaction potential of telaprevir with medications that are substrates, inhibitors, or inducers of cytochrome P450 (CYP) 3A4/5 and CYP1A, a list of currently marketed medications that could interact via these enzymes is presented in Addendum 2 of the protocol. For guidance on the use of medications concomitantly with Peg-IFN-alfa-2a (Pegasys), Peg-IFN-alfa-2b (PegIntron), or RBV (Copegus or Rebetol), the package inserts of these drugs were to be consulted.				

Assessments	
Antiviral Activity	Plasma samples for HCV RNA quantification were obtained at every trial visit, except at Follow-up Week 26. During the first week of treatment, intensive sampling for the quantification of HCV RNA (viral kinetics) was performed, i.e., at several time points on Day 1 (baseline) and on Day 2, and at a single time point on Days 3, 4, and 8. Plasma HCV RNA levels were measured using the COBAS TaqMan HCV test version 2.0 (lower limit of quantification 25 IU/mL). In this synopsis, the term 'undetectable HCV RNA' is used when no HCV RNA was detected in the plasma samples.
Viral Sequencing	Sequencing analyses (population sequencing) were typically conducted on baseline samples and breakthrough/relapse samples with HCV RNA levels above the limit of detection of the sequencing assay (~1,000 IU/mL). In addition, plasma samples for viral sequencing were taken for storage at all visits during the trial, except at Follow-up Week 26, and were analyzed upon request of the Protocol Virologist.
Pharmacokinetics	In a pharmacokinetic substudy, full pharmacokinetic profiles of telaprevir, VRT-127394 (R-diastereomer of telaprevir), and RBV were obtained over a 12-hour period in a subset of 15 subjects per treatment group on Day 1 and at Week 8 and Week 20 (only for RBV). The 12-hour postdose sample for telaprevir was not analyzed for telaprevir plasma concentration for subjects receiving telaprevir q8h. In the main study, blood samples were taken of all subjects for analysis of telaprevir, VRT-127394, RBV (plasma concentrations) and Peg-IFN (serum concentrations). This was performed at several time points on Day 1 (except for Peg-IFN for which only a predose sample was taken), at several time points on Day 2, at a single time point on Days 3, 4, and 8, at Weeks 2, 3, 4, 8, 12, 20 (only for determination of RBV and Peg-IFN concentrations), and EOT. At EOT, samples for determination of telaprevir and VRT-127394 concentrations were only taken for subjects who discontinued prematurely during telaprevir treatment.
Safety	
Adverse Events	All adverse events (AEs), serious and non-serious, were recorded at every visit up to and including the Follow-up Week 4 visit. After the Follow-up Week 4 visit, only at least possibly related serious AEs (SAEs) and at least possibly related grade 3 AEs were to be reported.
Clinical Laboratory	- Blood samples for hematology, coagulation, and serum chemistry measurements were taken at screening, at baseline, on Day 8, at Weeks 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, 24, 36, EOT, at Follow-up Weeks 4, 8, 12, and 24, and (in case of relapse) 24 weeks after relapse. At the baseline, Week 8, Week 20, and Follow-up Week 24 visits, a sample was to be collected with the subject in a fasting state, defined as an 8-hour, pre-sample fast. - Urine samples for urinalysis were taken at screening, baseline, Weeks 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, 24, 36, EOT, Follow-up Weeks 4, 8, 12, and 24, and (in case of relapse) 24 weeks after relapse.
Cardiovascular Safety	- Vital signs (pulse rate, systolic and diastolic blood pressure) were measured at screening, baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 36, EOT, and Follow-up Week 4. Additional monitoring of vital signs could be done if, in the opinion of the investigator, this was clinically indicated. - Standard 12-lead electrocardiograms (ECGs) were taken at screening, baseline (predose and 3 to 5 hours postdose), and the Week 2 visit (at any time of the day).
Physical Examination	A physical examination was performed at screening (including an eye examination), baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 36, EOT, and Follow-up Week 4.
Statistical Methods	All analyses were performed on the full analysis (FA) set, which was defined as all randomized subjects who received at least one dose of the study medication. An interim analysis was performed when all subjects had completed 12 weeks of treatment (or had discontinued earlier). The results of this interim analysis were presented at the Annual Meeting of American Association for the Study of Liver Diseases (AASLD; October 31 – November 4, 2008), and since the data were in the

	public domain, they were also shared with investigators during an investigator's meeting. The intention of the interim analysis was not to stop the current trial for any reason nor did it result in any protocol amendments. Therefore no multiplicity correction was considered. The final analysis was performed when all subjects had reached their Follow-up Week 24 visit or had discontinued earlier. In this synopsis, the results of the final analysis are presented. Note that not all data of one subject were included in this final analysis as this subject still had to attend the visit 24 weeks after relapse at the time of database lock (see table 'Main Features of the Subject Sample and Summary of the Results'). Demographic data and baseline characteristics were descriptively presented and tabulated per treatment group. Antiviral activity parameters that were explored, included viral response (i.e., either having undetectable HCV RNA or < 25 IU/mL HCV RNA [i.e., the subjects' plasma samples contained traces of HCV RNA at a concentration below the limit of quantification of the viral load assay or no HCV RNA was detected in the samples]), viral breakthrough, SVR24, and relapse. Viral breakthrough was defined as having a confirmed increase > 1 $\log_{10}$ in HCV RNA level from the lowest level reached, or a confirmed value of HCV RNA > 100 IU/mL in subjects whose HCV RNA had previously become < 25 IU/mL. Exact two-sided binomial 95% confidence intervals (CIs) were derived for all viral response parameters for each treatment group separately. Additionally, a logistic regression model was used to estimate the response rate for the different treatment groups and to estimate the 95% CI of the differences between treatments. This model included the continuous parameter baseline $\log_{10}$ HCV RNA and the stratification factor screening HCV genotype, and factors for telaprevir regimen (750 mg q8h or 1125 mg q12h) and Peg-IFN regimen (Pegasys or PegIntron). In addition, the interaction between the telaprevir and Peg-IFN regimen was tested using this model. If this interaction was not significant at the 10% significance level, the response rate of the telaprevir regimens (i.e., 750 mg q8h or 1125 mg q12h) was estimated by pooling subjects across both Peg-IFN regimens (i.e., Pegasys or PegIntron regimens). The response rate of the Peg-IFN regimens was also estimated by pooling subjects across both telaprevir regimens. For estimation and comparison in case of continuous variables, a similar analysis of variance (ANOVA) model was used and for time to event parameters a similar Cox proportional hazards model was used. The virology analysis focused on detecting previously characterized genotype 1 amino acid substitutions in the NS3 region associated with reduced susceptibility to telaprevir (V36A/M, T54A, R155I/K/M/T, and A156S/T/V) at baseline, viral breakthrough, or relapse. These amino acid substitutions confer either lower-level in vitro resistance to telaprevir (3- to 25-fold increase: single change V36A/M, T54A, R155I/K/M/T, and A156S) or higher-level in vitro resistance to telaprevir (> 50-fold increase: single change A156V/T and double change V36M+R155K). The incidence of amino acid substitutions at baseline and at the above time points was tabulated/listed. Further analyses aimed at identifying new amino acid substitutions associated with reduced susceptibility to telaprevir selected when failing a telaprevir-containing regimen are pending. In the pharmacokinetic substudy, descriptive statistics were calculated for the plasma concentrations of telaprevir, VRT-127394, and RBV and for derived pharmacokinetic parameters. Plasma concentration-time data were graphically presented. Pharmacokinetic parameters were subjected to an exploratory graphical analysis including various transformations in order to get a general overview. Statistical analysis was performed for RBV, comparing Week 20 (test) versus Week 8 (reference). The least square (LS) means of the pharmacokinetic parameters of RBV

	for each treatment were estimated with a linear mixed effects model, controlling for treatment as fixed effect and subject as a random effect. A 90% CI was constructed around the difference between the LSmeans of test and reference. The statistical analysis for RBV comparing Week 20 versus Week 8 was performed separately for the pooled P(2a)R and P(2b)R treatment groups. Only subjects for whom no dose modifications or dose interruptions for RBV were reported were included in this analysis. A statistical analysis was performed for telaprevir and VRT-127394, comparing maximum plasma concentrations (C_{max}) and areas under the plasma concentration versus time curves from time of administration up to 24 hours (AUC_{24h}) (Day 1 and Week 8) and minimum plasma concentrations (C_{min}) (Week 8 only) for the q12h dosing regimen with the q8h dosing regimen, separately for the P(2a)R and P(2b)R treatment groups. The LSmeans of the pharmacokinetic parameters of telaprevir and VRT-127394 for each treatment were estimated with a linear mixed effects model, controlling for the dosing regimen (q12h or q8h) as fixed effect and subject as a random effect. A 90% CI was constructed around the difference between the LSmeans of test and reference. In the main study, individual estimates of telaprevir predose plasma concentrations (C_{0h}), C_{max}, and AUC_{24h} were assessed by means of sparse sampling using Bayesian feedback. Descriptive statistics were calculated for the telaprevir C_{0h}, C_{max}, and AUC_{24h}, the predose plasma concentrations of RBV, the serum concentrations of Peg-IFN-alfa-2a and Peg-IFN-alfa-2b, and for the AUC_{Week1} of Peg-IFN-alfa-2a and Peg-IFN-alfa-2b. The predose concentrations were graphically displayed as well. Safety data summaries were provided for AEs, laboratory data, ECG, and vital signs. Pharmacokinetic-pharmacodynamic relationships with regards to both efficacy and safety were evaluated for telaprevir based on the individual estimates of the telaprevir pharmacokinetic parameters in the main study (C_{0h} and AUC_{24h} for efficacy and C_{max} and AUC_{24h} for safety).

Main Features of the Subject Sample and Summary of the Results

Subject Disposition	T12(q8h)/ P(2a)R	T12(q8h)/ P(2b)R	T12(q12h)/ P(2a)R	T12(q12h)/ P(2b)R
Number of subjects treated[a]	40	42	40	39
Number (%) of subjects who				
discontinued treatment prior to Week 24 for any reason	4 (10.0)	4 (9.5)	7 (17.5)	8 (20.5)
were assigned to 24 weeks of treatment[b] and completed treatment	30 (75.0)	28 (66.7)	29 (72.5)	22 (56.4)
were assigned to 48 weeks of treatment and				
a) completed treatment	4 (10.0)	6 (14.3)	3 (7.5)	6 (15.4)
b) discontinued treatment between Week 24 and 48 for any reason	2 (5.0)	4 (9.5)	1 (2.5)	3 (7.7)
Total number (%) of subjects who discontinued all study medication	6 (15.0)	8 (19.0)	8 (20.0)	11 (28.2)
Reason				
Adverse event	3 (7.5)	2 (4.8)	4 (10.0)	4 (10.3)
Subject ineligible to continue the trial	0	0	0	1 (2.6)
Subject noncompliant	1 (2.5)	3 (7.1)	1 (2.5)	2 (5.1)
Subject reached a virologic endpoint	1 (2.5)	3 (7.1)	2 (5.0)	4 (10.3)
Subject withdrew consent	1 (2.5)	0	1 (2.5)	0
Total number (%) of subjects who discontinued the trial	3 (7.5)	3 (7.1)	2 (5.0)	3 (7.7)
Reason				
Subject ineligible to continue the trial	0	0	0	1 (2.6)
Subject lost to follow-up	0	0	1 (2.5)	1 (2.6)
Subject withdrew consent	3 (7.5)	2 (4.8)	1 (2.5)	1 (2.6)
Other	0	1 (2.4)	0	0
Ongoing[c]	0	0	1 (2.5)	0

[a] Five additional subjects were randomized, but were not treated. Four of these subjects (1 randomized to T12(q8h)/P(2a)R, 1 randomized to T12(q12h)/P(2a)R, and 2 randomized to T12(q12h)/P(2b)R) were found ineligible to continue the trial before first intake of study medication and 1 of these subjects (randomized to T12(q12h)/P(2a)R) withdrew consent before first intake of study medication.

[b] Subjects' HCV RNA was undetectable from Week 4 through Week 20.

[c] Note that all subjects had either completed or discontinued the trial prematurely when the database was locked (20 August 2009), except for one subject who still had to attend the visit 24 weeks after relapse. This visit took place on 14 September 2009.

Demographic and Baseline Characteristics	**T12(q8h)/ P(2a)R N = 40**	**T12(q8h)/ P(2b)R N = 42**	**T12(q12h)/ P(2a)R N = 40**	**T12(q12h)/ P(2b)R N = 39**
Sex, n (%)				
Female	20 (50.0)	22 (52.4)	19 (47.5)	20 (51.3)
Male	20 (50.0)	20 (47.6)	21 (52.5)	19 (48.7)
Race[a], n (%)				
Black	2 (5.0)	1 (2.4)	1 (2.5)	1 (2.6)
Caucasian/white	36 (90.0)	38 (90.5)	36 (90.0)	35 (92.1)
Oriental/Asian	1 (2.5)	1 (2.4)	2 (5.0)	0
Other	1 (2.5)	2 (4.8)	1 (2.5)	2 (5.3)
Age (years)				
Median (Range)	46.5 (23; 63)	45.5 (20; 65)	40.0 (22; 61)	49.0 (19; 63)
BMI (kg/m^2)				
Median (Range)	23.4 (19; 35)	23.9 (20; 37)	23.8 (18; 34)	24.7 (20; 46)
Baseline log_{10} HCV RNA (log_{10} IU/mL)				
Median (Range)	6.4 (5; 7)	6.7 (5; 7)	6.5 (5; 7)	6.7 (4; 8)
Assessment of liver histology and fibrosis, n (%)				
Cirrhosis	1 (2.5)	1 (2.4)	0	2 (5.1)
Bridging fibrosis	8 (20.0)	10 (23.8)	7 (17.5)	12 (30.8)
Portal fibrosis	16 (40.0)	16 (38.1)	11 (27.5)	13 (33.3)
No or minimal fibrosis	15 (37.5)	15 (35.7)	22 (55.0)	11 (28.2)
Other	0	0	0	1 (2.6)
HCV genotype (NS3)[b], n (%)				
1a	21 (52.5)	23 (54.8)	21 (52.5)	17 (43.6)
1b	18 (45.0)	19 (45.2)	19 (47.5)	22 (56.4)
1c	1 (2.5)	0	0	0

N: number of subjects with data; n: number of subjects with that observation

[a] The race of one subject from the T12(q12h)/P(2b)R group was unknown.

[b] The subtype was also determined with the 5'NC – Trugene genotyping method performed by the central laboratory and with an HCV genotyping method based on sequencing of a 329-bp region within NS5B followed by semi-automatic blast based alignment to reference sequences. The results are shown in Section 4.1.4.

Antiviral Activity	**T12(q8h)/ P(2a)R N = 40**	**T12(q8h)/ P(2b)R N = 42**	**T12(q12h)/ P(2a)R N = 40**	**T12(q12h)/ P(2b)R N = 39**
SVR24[a], n (%)	34 (85.0)	34 (81.0)	33 (82.5)	32 (82.1)
SVR24 (n/N[b] [%]) for subjects who				
discontinued treatment prior to Week 24	0/4 (0)	1/4 (25.0)	1/7 (14.3)	3/8 (37.5)
were assigned to 24 weeks of treatment[c] and completed treatment	29/30 (96.7)	26/28 (92.9)	29/29 (100)	21/22 (95.5)
were assigned to 48 weeks of treatment and				
a) completed treatment	4/4 (100)	5/6 (83.3)	2/3 (66.7)	6/6 (100)
b) discontinued treatment between Week 24 and 48	1/2 (50.0)	2/4 (50.0)	1/1 (100)	2/3 (66.7)
Log_{10} HCV RNA (log_{10} IU/mL), mean (SE)				
Baseline value	6.4 (0.09)	6.5 (0.10)	6.4 (0.09)	6.5 (0.11)
Change from baseline at Week 12[d]	-5.2 (0.24)	-5.4 (0.23)	-4.8 (0.36)	-5.1 (0.29)
Change from baseline at EOT[d]	-5.5 (0.14)	-5.2 (0.25)	-5.4 (0.22)	-5.3 (0.23)
Viral response (undetectable HCV RNA) rate, n (%)				
by Week 4 (i.e., RVR rate)[d]	32 (80.0)	29 (69.0)	33 (82.5)	26 (66.7)
by Week 12[d]	37 (92.5)	39 (92.9)	33 (82.5)	33 (84.6)
by EOT[d]	37 (92.5)	37 (88.1)	37 (92.5)	34 (87.2)
Time to first viral response (undetectable HCV RNA), median (days)	22	23	22	29
Cumulative viral breakthrough rate, n (%)	1 (2.5)	6 (14.3)	3 (7.5)	4 (10.3)
during the telaprevir treatment phase (i.e., during treatment with telaprevir, Peg-IFN/RBV)	1 (2.5)	3 (7.1)	2 (5.0)	3 (7.7)
after the telaprevir treatment phase, during treatment with Peg-IFN/RBV	0	3 (7.1)	1 (2.5)	1 (2.6)
Relapse[a], n/N[e] (%)	3/37 (8.1)	2/37 (5.4)	3/37 (8.1)	1/34 (2.9)

N: number of subjects with data; n: number of subjects with that observation; SE: standard error

[a] In addition to the subjects with SVR24 and relapse, there were 3 more subjects with undetectable HCV RNA at EOT (1 subject each in the T12(q8h)/P(2b)R, T12(q12h)/P(2a)R, and T12(q12h)/P(2b)R group). For these subjects no HCV RNA measurements were available during follow-up.

[b] Number of subjects with that treatment duration.

[c] Subjects' HCV RNA was undetectable from Week 4 through Week 20.

[d] NC = F imputed data

[e] N: number of subjects with undetectable HCV RNA at EOT.

Virology

The current analysis focused on detecting previously characterized genotype 1 amino acid substitutions in the NS3 region associated with reduced susceptibility to telaprevir (V36A/M, T54A, R155I/K/M/T, and A156S/T/V).

Only 1 subject with genotype 1a (based on NS3 genotyping method) had an amino acid substitution associated with reduced susceptibility to telaprevir at baseline, i.e., R155K. This subject had undetectable HCV RNA at EOT and achieved SVR24.

Of the 14 subjects with viral breakthrough, 11 had genotype 1a and 3 had genotype 1b (based on NS3 genotyping method). Most of the viral breakthroughs (i.e., 11 of the 14) were associated with viral variants carrying previously described amino acid substitutions associated with reduced susceptibility to telaprevir, mostly higher-level telaprevir resistant variants. In the other 3 subjects with viral breakthrough, no amino acid substitutions associated with reduced susceptibility to telaprevir were detected. Two of these 3 subjects had viral breakthrough after discontinuing telaprevir treatment (during continued treatment with Peg-IFN/RBV), while the third subject had viral breakthrough during treatment with telaprevir, Peg-IFN, and RBV.

Of the 9 subjects with relapse, 6 had genotype 1b and 3 had genotype 1a (based on NS3 genotyping method). Viral sequence analyses at the time of relapse were available for 7 of the 9 relapsers. In 6 of these 7 relapsers, relapse was associated with previously described amino acid substitutions associated with reduced susceptibility to telaprevir, mostly lower-level telaprevir resistant variants. In the 7th relapser, no amino acid substitutions associated with reduced susceptibility to telaprevir were detected.

Pharmacokinetics of telaprevir in pharmacokinetic substudy (mean ± SD)	**T12(q8h)/ P(2a)R (reference 1)**	**T12(q8h)/ P(2b)R (reference 2)**	**T12(q12h)/ P(2a)R (test 1)**	**T12(q12h)/ P(2b)R (test 2)**
Day 1				
N	14[a]	15[c]	12	12[f]
C_{max}, ng/mL	2025 ± 1119	2031 ± 650.0	2525 ± 1387	3061 ± 1154
AUC_{24h}, ng.h/mL	28040 ± 16530	24420 ± 7892	29530 ± 17300	38370 ± 15410
Day 57 (Week 8)				
N	6[b]	11[d]	10[e]	8[g]
C_{min}, ng/mL	2624 ± 507.2	2476 ± 329.0	2134 ± 620.2	2440 ± 516.8
C_{max}, ng/mL	4523 ± 768.3	4036 ± 727.6	4882 ± 783.5	4502 ± 1047
AUC_{24h}, ng.h/mL	85890 ± 17610	80420 ± 12440	81670 ± 20090	85550 ± 18300
	LSmeans ratio (90% CI)			
	Test 1 vs reference 1		**Test 2 vs reference 2**	
Day 1				
N	12 vs 14[a]		12[f] vs 15[c]	
C_{max}	1.32 (0.86 – 2.01)		1.48 (1.14 – 1.91)	
AUC_{24h}	1.17 (0.70 – 1.96)		1.53 (1.17 – 2.01)	
Day 57 (Week 8)				
N	10[e] vs 6[b]		8[g] vs 11[d]	
C_{min}	0.79 (0.63 – 0.99)		0.98 (0.86 – 1.11)	
C_{max}	1.08 (0.95 – 1.24)		1.11 (0.97 – 1.27)	
AUC_{24h}	0.94 (0.76 – 1.17)		1.06 (0.92 – 1.22)	

[a] N = 12 for AUC_{24h}
[b] N = 8 for C_{min} and C_{max}
[c] N = 13 for AUC_{24h}
[d] N = 13 for C_{min}, N = 16 for C_{max}
[e] N = 11 for C_{min} and C_{max}
[f] N = 11 for AUC_{24h}
[g] N = 9 for C_{min}, N = 11 for C_{max}

Pharmacokinetics of telaprevir in main study (population pharmacokinetics) (mean ± SD)	**T12(q8h)/ P(2a)R**	**T12(q8h)/ P(2b)R**	**T12(q12h)/ P(2a)R**	**T12(q12h)/ P(2b)R**
N	38	40	39	37
AUC_{24h}, ng.h/mL	89404 ± 20984	76627 ± 18509	82317 ± 19655	88493 ± 22298
C_{0h}, ng/mL	3197 ± 862	2723 ± 782	2474 ± 891	2682 ± 1043
C_{max}, ng/mL	4308 ± 918	3697 ± 781	4497 ± 869	4818 ± 1122

Pharmacokinetics of RBV in pharmacokinetic substudy (mean ± SD)	**T12(q8h)/ P(2a)R**	**T12(q8h)/ P(2b)R**	**T12(q12h)/ P(2a)R**	**T12(q12h)/ P(2b)R**
Day 57 (Week 8; test)				
N	8[a]	16[c]	9[e]	9[f]
C_{min}, ng/mL	2500 ± 1581	2564 ± 701.1	1952 ± 375.8	3356 ± 1028
C_{max}, ng/mL	3084 ± 1803	3684 ± 839.2	2627 ± 412.4	4532 ± 1462
AUC_{12h}, ng.h/mL	33520 ± 21200	36830 ± 8628	26650 ± 4840	47350 ± 14920
Day 141 (Week 20; reference)				
N	11[b]	13[d]	8	9[f]
C_{min}, ng/mL	1900 ± 796.8	2388 ± 757.5	1965 ± 285.5	2590 ± 1185
C_{max}, ng/mL	2458 ± 1108	3848 ± 821.5	2811 ± 602.1	3866 ± 1618
AUC_{12h}, ng.h/mL	25240 ± 11900	35690 ± 6434	28060 ± 4815	38240 ± 9795

	LSmeans ratio (90% CI) Day 57 (Week 8) vs Day 141 (Week 20)	
	P(2a)R[g]	**P(2b)R[g]**
N	15[h] vs 17[i]	22[j] vs 19[k]
C_{min}	1.12 (0.94 – 1.34)	1.16 (1.03 – 1.30)
C_{max}	1.09 (0.95 – 1.24)	1.01 (0.95 – 1.08)
AUC_{12h}	1.12 (0.95 – 1.33)	1.07 (1.00 – 1.15)

[a] N = 7 for C_{min} and AUC_{12h}
[b] N = 9 for C_{min}, N = 10 for AUC_{12h}
[c] N = 13 for C_{min}, N = 15 for AUC_{12h}
[d] N = 11 for AUC_{12h}
[e] N = 8 for AUC_{12h}
[f] N = 7 for AUC_{12h}
[g] P(2a)R represents the pooled T12(q8h)/P(2a)R and T12(q12h)/P(2a)R groups and P(2b)R represents the pooled T12(q8h)/P(2b)R and T12(q12h)/P(2b)R groups.
[h] N = 17 for C_{max}
[i] N = 16 for C_{min}
[j] N = 19 for C_{min}, N = 20 for AUC_{12h}
[k] N = 17 for AUC_{12h}

Safety						
Telaprevir treatment phase (i.e., from first intake of study medication until last dose of telaprevir) (N = number of subjects with data)	**T12(q8h)/ P(2a)R N = 40**	**T12(q8h)/ P(2b)R N = 42**	**T12(q12h)/ P(2a)R N = 40**	**T12(q12h)/ P(2b)R N = 39**	**T12(q8h)[e] N = 82**	**T12(q12h)[e] N = 79**
Adverse Events						
Most frequently reported AEs[a], n (%)						
Rash SSC[b]	29 (72.5)	21 (50.0)	22 (55.0)	20 (51.3)	50 (61.0)	42 (53.2)
Pruritus SSC[b]	16 (40.0)	23 (54.8)	20 (50.0)	22 (56.4)	39 (47.6)	42 (53.2)
Nausea	18 (45.0)	14 (33.3)	16 (40.0)	23 (59.0)	32 (39.0)	39 (49.4)
Anemia	18 (45.0)	14 (33.3)	14 (35.0)	20 (51.3)	32 (39.0)	34 (43.0)
Influenza-like illness	15 (37.5)	19 (45.2)	11 (27.5)	20 (51.3)	34 (41.5)	31 (39.2)
n (%) with 1 or more AEs	40 (100)	41 (97.6)	40 (100)	39 (100)	81 (98.8)	79 (100)
n (%) of deaths	0	0	0	0	0	0
n (%) with 1 or more other SAEs	5 (12.5)	1 (2.4)	4 (10.0)	1 (2.6)	6 (7.3)	5 (6.3)
n (%) of permanent discontinuation of telaprevir due to 1 or more AEs	8 (20.0)	3 (7.1)	8 (20.0)	6 (15.4)	11 (13.4)	14 (17.7)
n (%) with 1 or more grade 3 AEs	12 (30.0)	8 (19.0)	15 (37.5)	10 (25.6)	20 (24.4)	25 (31.6)
n (%) with 1 or more AEs at least possibly related to telaprevir[c]	39 (97.5)	37 (88.1)	36 (90.0)	39 (100)	76 (92.7)	75 (94.9)
Overall treatment phase (N = number of subjects with data)	**T12(q8h)/ P(2a)R N = 40**	**T12(q8h)/ P(2b)R N = 42**	**T12(q12h)/ P(2a)R N = 40**	**T12(q12h)/ P(2b)R N = 39**	**P(2a)R[e] N = 80**	**P(2b)R[e] N = 81**
Adverse Events						
Most frequently reported AEs[d], n (%)						
Rash SSC[b]	29 (72.5)	24 (57.1)	23 (57.5)	22 (56.4)	52 (65.0)	46 (56.8)
Pruritus SSC[b]	19 (47.5)	24 (57.1)	21 (52.5)	25 (64.1)	40 (50.0)	49 (60.5)
Nausea	18 (45.0)	14 (33.3)	16 (40.0)	23 (59.0)	34 (42.5)	37 (45.7)
Anemia	18 (45.0)	14 (33.3)	18 (45.0)	20 (51.3)	36 (45.0)	34 (42.0)
Headache	13 (32.5)	21 (50.0)	16 (40.0)	17 (43.6)	29 (36.3)	38 (46.9)
Influenza-like illness	16 (40.0)	19 (45.2)	11 (27.5)	20 (51.3)	27 (33.8)	39 (48.1)
Asthenia	14 (35.0)	18 (42.9)	9 (22.5)	15 (38.5)	23 (28.8)	33 (40.7)
n (%) with 1 or more AEs	40 (100)	41 (97.6)	40 (100)	39 (100)	80 (100)	80 (98.8)
n (%) of deaths	0	0	0	0	0	0
n (%) with 1 or more other SAEs	8 (20.0)	2 (4.8)	6 (15.0)	4 (10.3)	14 (17.5)	6 (7.4)
n (%) with 1 or more grade 3 AEs	16 (40.0)	14 (33.3)	16 (40.0)	13 (33.3)	32 (40.0)	27 (33.3)

[a] reported in > 40% of subjects in the pooled T12(q8h) or T12(q12h) group
[b] Special search categories (SSCs) for rash-, pruritus-, and ano-rectal-related AEs were created to ensure all clinically similar events were tabulated and analyzed.
[c] In the overall treatment phase, the same number of subjects had at least 1 AE at least possibly related to telaprevir.
[d] reported in > 40% of subjects in the pooled P(2a)R or P(2b)R group
[e] T12(q8h) represents the pooled T12(q8h)/P(2a)R and T12(q8h)/P(2b)R groups and T12(q12h) represents the pooled T12(q12h)/P(2a)R and T12(q12h)/P(2b)R groups. P(2a)R represents the pooled T12(q8h)/P(2a)R and T12(q12h)/P(2a)R groups and P(2b)R represents the pooled T12(q8h)/P(2b)R and T12(q12h)/P(2b)R groups.

Adverse Events	No deaths were reported. During the telaprevir treatment phase, the most frequently reported AEs in the pooled T12(q8h) and T12(q12h) groups were rash SSC, pruritus SSC, nausea, anemia, and influenza-like illness. Grade 3 AEs (mainly anemia and leukopenia) occurred in 20 (24.4%) subjects in the pooled T12(q8h) group and in 25 (31.6%) subjects in the pooled T12(q12h) group. Serious AEs (mainly anemia and rash) occurred in 6 (7.3%) subjects in the pooled T12(q8h) group and in 5 (6.3%) subjects in the pooled T12(q12h) group. Adverse events that led to permanent discontinuation of telaprevir (mainly rash, pruritus, anemia, and vomiting) were reported in 11 (13.4%) subjects in the pooled T12(q8h) group and in 14 (17.7%) subjects in the pooled T12(q12h) group. Adverse events considered at least possibly related to telaprevir treatment were reported in the majority of subjects. The most frequent at least possibly related AEs were nausea, pruritus, and rash. Few SSC events (pruritus SSC, rash SSC, and ano-rectal SSC events) occurring during the telaprevir treatment phase were serious. Most SSC events were grade 1 or 2 in severity. Grade 3 pruritus SSC events and rash SSC events were each observed in at most 3 subjects in either the pooled T12(q8h) or pooled T12(q12h) group. None of the subjects had grade 3 ano-rectal SSC events. Pruritus SSC events leading to permanent discontinuation of telaprevir were reported for 3 (3.7%) subjects in the pooled T12(q8h) group and for 4 (5.1%) subjects in the pooled T12(q12h) group and rash SSC events leading to permanent discontinuation of telaprevir were reported for 7 (8.5%) subjects and 6 (7.6%) subjects, respectively. There were no ano-rectal SSC events that led to permanent discontinuation of telaprevir. During the overall treatment phase, the most frequently reported AEs in the pooled P(2a)R and P(2b)R groups included those mentioned for the telaprevir treatment phase, as well as asthenia and headache. Grade 3 AEs (mainly anemia, leukopenia, blood uric acid increased, and rash) occurred in 32 (40.0%) and 27 (33.3%) subjects in the pooled P(2a)R and P(2b)R groups, respectively. Serious AEs in the overall treatment phase were more frequent in the pooled P(2a)R group than in the pooled P(2b)R group (14 [17.5%] versus 6 [7.4%] subjects). The most frequently reported SAEs were the same as in the telaprevir treatment phase, i.e., anemia and rash. The most common AE leading to permanent discontinuation of Peg-IFN and/or RBV was rash. Few SSC events (pruritus SSC, rash SSC, and ano-rectal SSC events) occurring during the overall treatment phase were serious. Most SSC events were grade 1 or 2 in severity.

Clinical Laboratory Tests	A mean decrease in AST levels (ranging from -32.7 to -22.6 U/L in the 4 treatment groups) and ALT levels (ranging from -65.7 to -47.5 U/L) was observed within the first 2 weeks of treatment. Thereafter the AST and ALT levels remained more or less constant. A mean decrease in hemoglobin level was observed in all treatment groups until Week 8, 10, or 12. This decrease ranged from -45.4 to -37.5 g/L and was followed by a small increase after Week 12. The most frequently reported (in more than 25% of subjects in the pooled T12(q8h) or pooled T12(q12h) group) graded treatment-emergent laboratory abnormalities during the telaprevir treatment phase were increases in uric acid, hypophosphatemia, decreases in WBC count, hemoglobin, neutrophils, lymphocytes, and platelet count, hypertriglyceridemia, and hyperbilirubinemia (total). Increased uric acid, decreased WBC count, hemoglobin, neutrophils, and lymphocytes were also the most frequent (in more than 10% of subjects in at least one of the pooled groups) treatment-emergent toxicities of grade 3. The laboratory abnormality most frequently reported as AE during the telaprevir treatment phase was anemia, which was reported as AE in 39.0% and 43.0% of subjects in the pooled T12(q8h) and pooled T12(q12h) group, respectively. Other laboratory abnormalities reported as AE in more than 10% of subjects in either of these groups were leukopenia, lymphopenia, and blood uric acid increased. During the overall treatment phase, the most frequently observed graded laboratory abnormalities were the same as in the telaprevir treatment phase. Neutropenia was reported as AE during the overall treatment phase in more than 10% of subjects in the pooled P(2a)R or pooled P(2b)R group in addition to anemia, leukopenia, and lymphopenia, and blood uric acid increased.
Cardiovascular Safety	Median changes from baseline in vital signs parameters were generally small. None of the median changes were considered clinically relevant. Adverse events related to vital signs were reported for only a few subjects. Median changes from baseline in ECG parameters were generally small. None of the median changes were considered clinically relevant. None of the subjects had a QTcF value above 500 ms. One (2.6%) subject in the T12(q12h)/P(2b)R group had a QTcF between 480 and 500 ms and 1 (2.4%) subject in the T12(q8h)/P(2b)R group had a QTcF between 450 and 480 ms. ECG abnormalities other than QT increases were infrequent. A small number of subjects had an abnormality in ECG parameters that was reported as AE.

Relationships between telaprevir pharmacokinetics and viral response	Given the low number of non-responders in this trial, no firm conclusions can be drawn for the relationship between telaprevir pharmacokinetics and viral response.
Relationships between telaprevir pharmacokinetics and safety	A trend towards a positive relationship between the exposure (AUC_{24h} and C_{max}) to telaprevir and the severity of rash SSC events and grades of treatment-emergent hemoglobin abnormalities was observed. It should, however, be noted that very low numbers of subjects experienced a grade 3 rash SSC event.

Conclusions

In the present trial, the efficacy, safety, tolerability, pharmacokinetics, and pharmacokinetic-pharmacodynamic relationships of telaprevir were explored when administered as 750 mg q8h or 1125 mg q12h in combination with Peg-IFN-alfa-2a (Pegasys®) and RBV (Copegus®) or Peg-IFN-alfa-2b (PegIntron®) and RBV (Rebetol®).

The trial has shown the following:

- SVR24 rates were similar in all 4 treatment groups (81.0 to 85.0%).

  At Week 4, 66.7 to 82.5% of the subjects had undetectable HCV RNA. These percentages had increased to 82.5-92.9% at Week 12 and to 87.2%-92.5% at EOT. There were no significant differences between the 4 treatment groups.

  Viral breakthrough and relapse were infrequent.

  Fourteen subjects had viral breakthrough, of whom 11 had genotype 1a and 3 had genotype 1b (based on NS3 genotyping method). Most of the viral breakthroughs (i.e., 11 of the 14) were associated with viral variants carrying previously described amino acid substitutions associated with reduced susceptibility to telaprevir, mostly higher-level telaprevir resistant variants. In the other 3 subjects with viral breakthrough, no amino acid substitutions associated with reduced susceptibility to telaprevir were detected. Two of these 3 subjects had viral breakthrough after discontinuing telaprevir treatment (during continued treatment with Peg-IFN/RBV), while the third subject had viral breakthrough during treatment with telaprevir, Peg-IFN, and RBV.

  Nine subjects had relapse, of whom 6 had genotype 1b and 3 had genotype 1a (based on NS3 genotyping method). Viral sequence analyses at the time of relapse were available for 7 of the 9 relapsers. In 6 of these 7 relapsers, relapse was associated with previously described amino acid substitutions associated with reduced susceptibility to telaprevir, mostly lower-level telaprevir resistant variants. In the 7th relapser, no amino acid substitutions associated with reduced susceptibility to telaprevir were detected.
- In the pharmacokinetic substudy, steady-state telaprevir C_{max} was comparable for the q12h versus the q8h dosing regimen in the P(2a)R treatment groups (90% CI of the LSmeans ratio was within 0.80-1.25) and 11% higher for the q12h dosing regimen in the P(2b)R treatment groups. Telaprevir C_{min} was 21% lower for the q12h dosing regimen in the P(2a)R treatment groups, while values were comparable in the P(2b)R treatment groups. The telaprevir AUC_{24h} was 6% lower for the q12h regimen compared to the q8h regimen in the P(2a)R treatment groups. For the P(2b)R treatment groups, AUC_{24h} was comparable for the q12h and q8h regimens. The population pharmacokinetic data for telaprevir were consistent with the results of the pharmacokinetic substudy.
- A trend towards a positive relationship between the exposure to telaprevir and the severity of rash SSC events and grades of treatment-emergent hemoglobin abnormalities was observed. It should, however, be noted that very low numbers of subjects experienced a grade 3 rash SSC event.
- Overall, telaprevir was generally well-tolerated. The most frequently reported AEs during the telaprevir treatment phase were rash SSC, pruritus SSC, nausea, anemia, and influenza-like illness. The overall safety profile was similar in all 4 treatment groups.

In conclusion, the current trial showed similar SVR24 rates (81.0-85.0%) when telaprevir was dosed q8h or q12h, and in combination with either Peg-IFN-alfa-2a or Peg-IFN-alfa-2b.

Disclaimer

Disclaimer Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.