SYNOPSIS

Protocol Summary

Company: Tibotec BVBA **Trade Name**: - **Indication**: Chronic hepatitis C virus infection	**Drug Substance**: VX-950 (telaprevir) **Trial no**.: VX-950-TiDP24-C210 **Clinical Phase**: IIa
Title: A Phase IIa randomized, partially blinded trial of telaprevir (VX-950) in treatment-naïve subjects with chronic genotype 4 hepatitis C infection	
Investigator: [redacted], M.D., Groupe Hospitalier Pitiè Salpetrière, Service d'Hepato-Gastro-Entérologie, [redacted] France	**Country**: France
Trial Period: Start: 3-Jan-2008 End: 11-Jan-2010 Note that the date of last contact in the statistical output was 5 January 2010, corresponding to the last visit of any subject in the trial. The trial ended on 11 January 2010, when the last subject was considered lost to follow-up.	**No. of Investigators**: 1 **No. of Subjects**: 24

Objectives: The primary objective of this trial was to assess the activity of telaprevir on hepatitis C virus (HCV) genotype 4 replication by evaluating early viral kinetic parameters, when administered during 2 weeks, alone or in combination with Peg-IFN-alfa-2a and RBV.

Secondary objectives were

- to evaluate the single-dose and steady-state pharmacokinetics of telaprevir and VRT-127394 and the pharmacokinetic/pharmacodynamic relationship of telaprevir in subjects chronically infected with HCV genotype 4;
- to evaluate the pharmacokinetics of Peg-IFN-alfa-2a and RBV, alone and in combination with telaprevir;
- to assess and characterize pheno- and genotypically viral variants potentially arising during 2 weeks of telaprevir treatment (with or without Peg-IFN-alfa-2a and RBV), during the 48-week standard treatment phase, and during the 24-week follow-up phase in subjects chronically infected with HCV genotype 4;
- to evaluate the safety and tolerability of a 2-week treatment with telaprevir with or without Peg-IFN-alfa-2a and RBV in subjects chronically infected with HCV genotype 4.

Design:

This was a Phase IIa partially blinded, randomized, multiple dose trial to assess the activity of telaprevir on hepatitis C virus (HCV) early viral kinetics in treatment-naïve subjects who were chronically infected with HCV genotype 4.

The trial consisted of a screening period of maximum 6 weeks, a 2-week investigational treatment phase, a 46- or 48-week standard treatment phase, and a follow-up period of at least 24 weeks (maximum 48 weeks).

A total of 24 treatment-naïve HCV genotype 4-infected subjects were to be enrolled in the trial. The subjects were randomized in a 1:1:1 ratio to 1 of 3 treatment groups:

- A. telaprevir 750 mg every 8 hours (q8h) (N = 8)
- B. telaprevir 750 mg q8h + pegylated interferon alfa-2a (Peg-IFN-alfa-2a) 180 µg once-weekly + ribavirin (RBV) 1,000-1,200 mg/day (weight-based) (N = 8)
- C. placebo q8h + Peg-IFN-alfa-2a 180 µg once-weekly + RBV 1,000-1,200 mg/day (weight-based) (N = 8)

All subjects were to receive the investigational treatment to which they were randomized for 2 weeks. Subsequently, subjects in Group A were to receive 48 weeks of standard therapy (i.e., until Week 50), consisting of Peg-IFN-alfa-2a 180 µg once-weekly and RBV 1,000-1,200 mg/day (weight-based) whereas subjects in Groups B and C had already been receiving standard therapy during the 2-week investigational treatment phase and were to continue standard therapy until they had received 48 weeks of standard therapy.

After the end of treatment (EOT, i.e., either having completed treatment or having discontinued all study medication earlier), all subjects were to be followed for at least 24 weeks. If at any time during the follow-up period a subject experienced relapse, the subject was not to 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).

HCV ribonucleic acid (RNA) quantification and safety/tolerability assessments were performed frequently throughout the trial. Extensive virologic and pharmacokinetic assessments for pharmacokinetic/pharmacodynamic analyses were performed during the investigational treatment phase.

Subject Selection

Inclusion Criteria

1. Male and female subjects, 18 to 65 years of age, inclusive.
2. Subject was to have chronic genotype 4 hepatitis C infection. Chronic disease status was to be confirmed by a diagnosis of hepatitis C > 6 months before the screening period.
3. Plasma HCV RNA level at screening was to be > 10,000 international units (IU)/mL.
4. Subject was never to have received treatment for HCV (including investigational products).
5. Screening laboratory values of the following variables were to meet the acceptable values defined below:

Laboratory variable	Acceptable values
Absolute neutrophil count	$\geq 1{,}500/mm^3$
Platelet count	$\geq 100{,}000/mm^3$
Hemoglobin	Within normal range

   All other hematology and biochemistry results were to show no clinically significant abnormalities, in the opinion of the investigator.
6. Subject was to be in good health (besides HCV infection), in the opinion of the investigator, judged on the basis of medical history and physical examination (including vital signs and screening electrocardiogram [ECG]), with any chronic medical conditions under stable medical control.
7. If heterosexually active, female subject of childbearing potential was to agree to the use of 2 effective methods of contraception from screening until 4 months after the last dose of RBV.

   If heterosexually active, non-vasectomized male subject with a female partner of childbearing potential was to agree to the use of 2 effective methods of contraception from screening until 7 months after the last dose of RBV.

   Note: Hormonal contraceptives may not be reliable when taking telaprevir. Therefore, in order to be eligible for this trial, female subjects were to use 2 barrier methods during telaprevir/placebo treatment and the subsequent month. Barrier contraceptives included but were not limited to the following methods: male condom, diaphragm with spermicidal gel, 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 condoms could cause the condoms to tear). As of 1 month after completion of telaprevir/placebo 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 sexual 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 2 years.
8. Subject had to be willing to refrain from the concomitant use of any disallowed medications or substances as mentioned in the protocol.
9. Subject was to have signed the informed consent form (ICF) voluntarily before the first trial-related activity.

Exclusion Criteria

1. Subject had a concomitant medical condition that in the opinion of the investigator could influence the results of the trial or could represent an additional risk for the administration of the study medication to the subject.
2. Subject had medical contraindications to the administration of an IFN (Peg-IFN-alfa-2a in particular) or RBV treatment, including but not limited to:
   - abnormal thyroid-stimulating hormone (TSH) levels or poorly controlled thyroid function;
   - evidence of clinically significant cardiac dysfunction;
   - history of psychiatric disorders determined by the investigator to contraindicate the use of IFN-based therapy;
   - evidence of autoimmune disease;
   - history of hemoglobinopathies
3. Subject had a history or evidence of cirrhosis, end-stage or decompensated liver disease, or hepatocellular carcinoma as shown by screening laboratory results of any of the following:
   - international normalized ratio (INR) ≥ 1.7;
   - serum albumin < 3.5 g/dL;
   - serum total bilirubin > 1.8 times the upper limit of laboratory normal range (ULN), unless isolated and for subjects with Gilbert's Syndrome;
   - history of ascites, hepatic encephalopathy, or bleeding esophageal varices;

- alfa-fetoprotein (AFP) > 50 ng/mL, unless absence of a mass could be documented on an ultrasound or magnetic resonance imaging (MRI) within the screening period.

4. Subject had a history or suspicion of alcohol, barbiturate, or amphetamine recreational or narcotic drug use, which in the investigator's opinion would compromise the subject's safety and/or compliance with study procedures.
5. Subject had human immunodeficiency virus (HIV) or hepatitis B virus (HBV) co-infection.
6. Women who were pregnant, breastfeeding, or planning to become pregnant and partners of women who were pregnant or breastfeeding.
7. Subject had hypersensitivity to tartrazine.
8. Subject participated in any clinical trial for an investigational drug within 90 days before drug administration or participated in more than 2 drug studies in the 12 months prior to screening (exclusive of the current trial).

Treatment	Telaprevir	Placebo	Peg-IFN-alfa-2a (Pegasys®)	RBV (Copegus®)
Concentration Dosage Form (F No.) Usage	375 mg tablet (F004) oral	- tablet (F003) oral	180 µg solution injection	200 mg tablet oral
Batch Numbers	3060433R	3061197R	B1059	92069
Dose Regimen	Subjects were randomized in a 1:1:1 ratio to 1 of 3 treatment groups (treatment labels are mentioned between brackets): A. (T2&PR48): telaprevir 750 mg q8h, orally from Day 1 to 15[a]; Peg-IFN-alfa-2a 180 µg once-weekly, subcutaneous injection + RBV 1,000-1,200 mg/day[b], orally from Day 15 to Week 50. B. (T2/PR48): telaprevir 750 mg q8h, orally from Day 1 to 15[a]; Peg-IFN-alfa-2a 180 µg once-weekly, subcutaneous injection + RBV 1,000-1,200 mg/day[b], orally from Day 1 to Week 48. C. (Pbo/PR48): placebo q8h, orally from Day 1 to 15[a]; Peg-IFN-alfa-2a 180µg once-weekly, subcutaneous injection + RBV 1,000-1,200 mg/day[b], orally from Day 1 to Week 48. [a] On Day 15, morning dose only [b] RBV dosing was weight-based: < 75 kg = 1,000 mg, ≥ 75 kg = 1,200 mg			
Duration of Treatment	All subjects were to receive the investigational treatment (telaprevir or placebo) to which they were randomized for 2 weeks. Subsequently, subjects in the T2&PR48 group were to receive 48 weeks of standard therapy (Peg-IFN-alfa-2a and RBV), whereas subjects in the T2/PR48 and Pbo/PR48 groups had already been receiving standard therapy during the 2-week investigational treatment phase and were to continue this therapy until they had received 48 weeks of standard therapy in total.			
Duration of Trial	Screening: maximum 6 weeks Treatment: up to 50 weeks Follow-up: at least 24 weeks (maximum 48 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®) or RBV (Copegus®), 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. On Days 1 and 2, multiple samples for viral kinetics were taken. 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 target was detected in the plasma samples.
Viral Sequencing	Sequencing analyses were typically conducted on baseline samples and viral breakthrough/relapse samples with HCV RNA levels above the limit of detection of the sequencing assay (~1,000 IU/mL). Upon Protocol Virologist's request, samples collected and stored at other time points could be analyzed.
Pharmacokinetics	Multiple samples for pharmacokinetic evaluation of telaprevir and VRT-127394 were taken on Days 1 (8 samples), 2 (2 samples), and 15 (8 samples). A single sample to assess the pharmacokinetics of telaprevir and VRT-127394 was taken on Days 3, 4, 8, and 12. Additionally, for subjects in the T2/PR48 and Pbo/PR48 groups, predose samples for pharmacokinetics of Peg-IFN-alfa-2a were taken on Days 1, 8, and 15. Additional samples for pharmacokinetics of Peg-IFN-alfa-2a were taken 24, 30, 48, and 72 hours after the Day 1 Peg-IFN-alfa-2a dosing. Also, for subjects in the T2/PR48 and Pbo/PR48 groups, predose samples for pharmacokinetics of RBV were taken on Days 1, 2, 3, 4, 8, and 15.
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, baseline, on Days 4, 8, and 15, at Weeks 6, 14, 26, 38, EOT for subjects in the T2&PR48 group and at screening, baseline, on Days 4, 8, and 15, Weeks 4, 12, 24, 36, EOT for subjects in the T2/PR48 and Pbo/PR48 groups. After EOT, in all subjects, samples were taken at Follow-up Weeks 4, 12, and 24, and (in case of relapse) 24 weeks after relapse. - At baseline, at Weeks 14, 26, and 38 (T2&PR48 group) or 12, 24, and 36 (T2/PR48 and Pbo/PR48 groups), and at EOT, 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, Days 2, 3, 4, 8, 15, Weeks 6, 14, 26, 38, EOT, and Follow-up Week 4 for subjects in the T2&PR48 group and at screening, baseline, Days 2, 3, 4, 8, 15, Weeks 4, 12, 24, 36, EOT, and Follow-up Week 4 for subjects in the T2/PR48 and Pbo/PR48 groups.
Cardiovascular Safety	- Vital signs (pulse rate, systolic and diastolic blood pressure) were measured at screening, baseline, Days 8 and 15, Weeks 6, 14, 26, 38, EOT, and Follow-up Week 4 for subjects in the T2&PR48 group and at screening, baseline, Days 8 and 15, Weeks 4, 12, 24, 36, EOT, and Follow-up Week 4 for subjects in the T2/PR48 and Pbo/PR48 groups. Additional monitoring of vital signs could be done if, in the opinion of the investigator, this was clinically indicated. - A standard 12-lead ECG was taken at screening, baseline (predose and 3 to 5 hours postdose), and Day 15 (at any time of the day).
Physical Examination	A physical examination was performed at screening (including an eye examination), baseline, Day 15, Weeks 6, 14, 26, 38, EOT, and Follow-up Week 4 for subjects in the T2&PR48 group and at screening (including an eye examination), baseline, Day 15, Weeks 4, 12, 24, 36, EOT, and Follow-up Week 4 for subjects in the T2/PR48 and Pbo/PR48 groups.

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. A primary analysis was performed when all randomized subjects had completed the 2-week investigational treatment to which they were randomized (i.e., the first 2 weeks of the treatment phase) or had discontinued earlier. The final analysis was performed once the trial was completed (i.e., all subjects had completed treatment and follow-up) and the database was locked. This synopsis presents the results of the final analysis. No formal statistical hypotheses were applicable for this trial. Results were descriptively presented and tabulated by treatment group. Demographic data and baseline characteristics were descriptively presented and tabulated per treatment group. Antiviral activity parameters that were investigated included viral response (either having undetectable HCV RNA or < 25 IU/mL HCV RNA), viral breakthrough (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), sustained viral response (SVR)12 (having undetectable HCV RNA at EOT and no confirmed detectable HCV RNA levels between EOT and 12 weeks after the last dose of study medication), SVR24 (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), and relapse (having confirmed detectable HCV RNA during the follow-up period in subjects who had undetectable HCV RNA at EOT). For all continuous variables, both absolute values and changes from baseline were analyzed descriptively and graphically presented. The binary response variables were tabulated. A longitudinal model was used to estimate the viral kinetics parameter epsilon. The virology analysis focused on detecting previously characterized HCV 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, relapse, or at the end of telaprevir treatment. The frequency 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. After completion of the bioanalysis and pharmacokinetic analyses, it was found that incorrect sample handling procedures had been followed, which resulted in unreliable results for RBV and VRT-127394 analyses. Pharmacokinetic results for RBV and VRT-127394 are therefore not discussed in this report. Descriptive statistics were calculated for the plasma concentrations of telaprevir 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 for telaprevir was performed by comparing the T2&PR48 group (reference) with the T2/PR48 group (test), by means of the following primary pharmacokinetic parameters: area under the plasma concentration-time curve over the dosing interval (AUC_{τ}) and maximum plasma concentration (C_{max}) (Days 1 and 15), and predose plasma concentration (C_{0h}) and minimum plasma concentration (C_{min}) (Day 15 only). The least square (LS) means of the primary parameters for the test and the reference groups were estimated with a linear mixed effects model controlling for treatment group as fixed effects. A 90% confidence interval (CI) was constructed around the difference between the LSmeans of test and reference. Both the difference between the LSmeans and the 90% CIs were retransformed to the original scale. Pharmacokinetic/pharmacodynamic relationships for telaprevir with regard to efficacy were graphically evaluated. Safety data summaries were provided for AEs, laboratory data, ECG, and vital signs.

Main Features of the Subject Sample and Summary of the Results

Subject Disposition - Baseline Characteristics	T2&PR48 N = 8	T2/PR48 N = 8	Pbo/PR48 N = 8	All Subjects N = 24
Number of subjects randomized (male/female)	5/3	6/2	4/4	15/9
Age: median (range), years	43.0 (36; 61)	41.0 (28; 52)	46.0 (30; 56)	45.5 (28; 61)
Body mass index (BMI): median (range), kg/m^2	24.3 (20; 35)	26.1 (21; 33)	28.0 (24; 37)	25.4 (20; 37)
Discontinuations[a], n (%)	6 (75.0)	1 (12.5)	3 (37.5)	10 (41.7)
Reasons:				
Subject reached a virologic endpoint	0	1 (12.5)	2 (25.0)	3 (12.5)
Adverse event	2 (25.0)	0	0	2 (8.3)
Subject lost to follow-up	2 (25.0)	0	0	2 (8.3)
Subject noncompliant	0	0	1 (12.5)	1 (4.2)
Other[b]	2 (25.0)	0	0	2 (8.3)

[a] Trial and treatment discontinuation were not recorded separately and are therefore presented together.
[b] One subject stopped treatment with the investigator's agreement; one subject discontinued treatment due to travel.

Antiviral Activity	T2&PR48		T2/PR48		Pbo/PR48	
	N	Value	N	Value	N	Value
Log_{10} HCV RNA (log_{10} IU/mL), median (range)						
Baseline value	8	5.83 (5.2; 6.5)	8	6.16 (5.4; 6.8)	8	5.88 (5.0; 6.8)
Change from baseline at Day 15	7	-0.77 (-2.9; 0.3)	8	-4.32 (-5.2; 0.0)	8	-1.58 (-4.0; -0.8)
Viral response (undetectable HCV RNA), n (%)						
by Day 15	7	0	8	1 (12.5)	8	0
by EOT	8	7 (87.5)	8	6 (75.0)	8	6 (75.0)
Time to first viral response (undetectable HCV RNA), median (days)	8	93	8	86	8	128
Cumulative viral breakthrough, n (%)						
by Day 15 (i.e., end of the telaprevir/placebo treatment phase)	8	5 (62.5)	8	0	8	0
by EOT	8	5 (62.5)	8	2 (25.0)	8	1 (12.5)
Sustained viral response (SVR), n (%)						
SVR12	8	6 (75.0)	8	4 (50.0)	8	5 (62.5)
SVR24	8	5 (62.5)[a]	8	4 (50.0)	8	5 (62.5)
Relapse, n (%)	7	1 (14.3)	6	2 (33.3)	6	1 (16.7)

N: number of subjects with data or, in case of relapse, number of subjects with undetectable HCV RNA at EOT;
n: number of subjects with that observation
[a] SVR24 was achieved by all the subjects who achieved SVR12, except for 1 (12.5%) subject in the T2&PR48 group who was considered as failure for SVR24. This subject (CRF ID [redacted]) was undetectable at Follow-up Week 12 but was lost to follow-up afterwards and therefore not a candidate for SVR24.

Virology

The current analysis focused on detecting previously characterized HCV 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).

None of the genotype 4 infected subjects had known amino acid substitutions associated with reduced susceptibility to telaprevir at baseline.

Sequences were available for 4 of the 5 subjects with viral breakthrough during telaprevir treatment. In 2 of the 4 subjects, a T54A/T mutation emerged during telaprevir treatment, while no known amino acid substitutions associated with reduced susceptibility to telaprevir were detected in the other 2 subjects. In the 2 subjects with viral breakthrough during Peg-IFN/RBV treatment in the T2/PR48 group, no known amino acid substitutions associated with reduced susceptibility to telaprevir were detected. A T54A/T mutation also emerged during telaprevir treatment in 2 other subjects who did not meet the definition of viral breakthrough, but who had detectable HCV RNA at the end of telaprevir treatment. All 4 telaprevir-treated subjects in whom a T54A/T mutation emerged achieved SVR24 with subsequent or continued Peg-IFN/RBV therapy.

For the 3 telaprevir-treated subjects with relapse, viral sequences were available at the time of relapse for 1 subject and at one or more later time points for the other 2 subjects. No known amino acid substitutions associated with reduced susceptibility to telaprevir were detected in these subjects.

Pharmacokinetics of telaprevir **Time point** Pharmacokinetic parameter (mean ± standard deviation [SD]), t_{max}: median [range])	**Telaprevir (reference)**	**Telaprevir + Peg-IFN-alfa-2a + RBV (test)**
Day 1		
N	8	8[b]
C_{max}, ng/mL	1,598 ± 803.1	1,709 ± 1,017
t_{max}, h	4.02 (3.00-5.97)	4.00 (3.00-6.00)
AUC_{8h}, ng.h/mL	6,702 ± 3,284	7,467 ± 4,684
Day 15		
N	7[a]	7[c]
C_{0h}, ng/mL	1,873 ± 376.6	2,806 ± 1,056
C_{min}, ng/mL	1,639 ± 447.7	2,100 ± 796.3
C_{max}, ng/mL	2,733 ± 554.9	3,669 ± 1,017
t_{max}, h	2.92 (0.00-4.08)	3.00 (1.92-4.00)
AUC_{8h}, ng.h/mL	17,120 ± 3,599	23,320 ± 7,065
$C_{ss,av}$, ng/mL	2,141 ± 438.5	2,896 ± 842.0
fluctuation index, %	51.99 ± 17.81	57.01 ± 21.71
LSmean ratio (90% CI)		
		Test vs reference
Day 1		
N	-	8 vs 8
C_{max}	-	1.00 (0.58 - 1.72)
AUC_{8h}[d]	-	0.98 (0.54 - 1.78)
Day 15		
N	-	7 vs 7
C_{0h}[e]	-	1.43 (1.02 - 2.02)
C_{min}	-	1.24 (0.88 - 1.74)
C_{max}	-	1.32 (1.05 - 1.66)
AUC_{8h}	-	1.33 (1.03 - 1.72)

t_{max}: time to reach the maximum plasma concentration; $C_{ss,av}$: average steady-state plasma concentration

[a] N = 6 for C_{0h}

[b] N = 7 for AUC_{8h}

[c] N = 5 for C_{0h}

[d] N = 7 for test

[e] N = 6 for reference and N = 5 for test

Pharmacokinetic/Pharmacodynamic Relationships	A trend towards a positive relationship between exposure to telaprevir (AUC_{8h}, C_{max}, and C_{min}) and decrease in log_{10} HCV RNA from Baseline to Day 15 was observed.

Safety (N: number of subjects in FA set)	**Telaprevir/Placebo Treatment Phase**			**Overall Treatment Phase[a]**		
	T2&PR48 N = 8	**T2/PR48 N = 8**	**Pbo/PR48 N = 8**	**T2&PR48 N = 8**	**T2/PR48 N = 8**	**Pbo/PR48 N = 8**
Adverse Events (AEs)						
Most frequently reported AEs[b], n (%)						
Infuenza-like illness	3 (37.5)	7 (87.5)	4 (50.0)	3 (37.5)	7 (87.5)	4 (50.0)
Asthenia	0	6 (75.0)	3 (37.5)	5 (62.5)	7 (87.5)	7 (87.5)
Headache	2 (25.0)	1 (12.5)	1 (12.5)	3 (37.5)	2 (25.0)	4 (50.0)
Pruritus SSC[c]	1 (12.5)	2 (25.0)	2 (25.0)	3 (37.5)	3 (37.5)	5 (62.5)
n (%) with 1 or more AEs	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)
n (%) of deaths	0	0	0	0	0	0
n (%) with 1 or more other SAEs	1 (12.5)	0	0	1 (12.5)	0	2 (25.0)
n (%) with 1 or more AEs leading to permanent discontinuation of telaprevir	1 (12.5)	0	0	1 (12.5)	0	0
n (%) with 1 or more grade 3 AEs	1 (12.5)	1 (12.5)	0	3 (37.5)	3 (37.5)	3 (37.5)
n (%) with 1 or more AEs at least possibly related to telaprevir	7 (87.5)	6 (75.0)	6 (75.0)	7 (87.5)	6 (75.0)	6 (75.0)
	No deaths were reported during the trial. One SAE (cholelithiasis) was reported in a subject in the T2&PR48 group and this SAE led to permanent stop of telaprevir. In addition, 2 subjects in the Pbo/PR48 group experienced an SAE (delirium and cholelithiasis) during Peg-IFN-alfa-2a/RBV treatment. Apart from the SAE cholelithiasis that led to permanent stop of telaprevir, no other AEs with action permanent stop of (any) study medication were reported during the telaprevir/placebo treatment phase. Two subjects in the T2&PR48 group and 1 subject in the Pbo/PR48 group had one or more AEs that led to permanent discontinuation of Peg-IFN-alfa-2a/RBV treatment. By preferred term, the most frequently reported AEs (in > 3 [37.5%] subjects in any treament group) during the telaprevir/placebo treatment phase were influenza-like illness and asthenia. Both were observed more often in subjects in the T2/PR48 group compared to in the other treatment groups. AEs in the system organ class 'gastrointestinal disorders' (mainly constipation, hemorrhoids, and nausea among others) were only observed in the treatment groups with telaprevir during the telaprevir/placebo treatment phase. No differences in incidences were noted for other AEs during that phase. During the telaprevir/placebo treatment phase, ano-rectal SSC events were reported in 3 (37.5%) subjects each in the treatment groups with telaprevir and in none of the subjects in the Pbo/PR48 group. Pruritus SSC events were observed in at most 2 (25.0%) subjects in any group during the telaprevir/placebo treatment phase; rash SSC events and anemia were observed in none of the subjects treated with telaprevir during that phase.					

[a] The overall treatment phase was from the date of first intake of telaprevir or placebo until the date of last study medication intake + 30 days

[b] Reported in > 3 (37.5%) subjects in any treatment group during the overall treatment phase

[c] Special search categories (SSCs) were created for rash-, pruritus-, ano-rectal-, and injection site reaction-related AEs by grouping AE terms that represent similar medical concepts, from the same or different system organ classes, to ensure that each subject with an event included within a pre-defined SSC was counted but counted only once.

Clinical Laboratory Tests	During the telaprevir/placebo treatment phase, the most frequent treatment-emergent graded toxicities (observed in more than 25.0% of subjects in any treatment group) were hypernatremia, increases in uric acid, and decreases in white blood cell (WBC) count, neutrophils, and platelet count. Emerging grade 3 toxicities in subjects who received telaprevir were decreased neutrophil count and increased gamma-glutamyltransferase (GGT), observed in 1 (12.5%) subject each during the telaprevir/placebo treatment phase. When considering overall treatment, treatment-emergent graded toxicities observed in more than 25.0% of subjects in any treatment group were those mentioned above as well as hypophosphatemia, decreases in hemoglobin and lymphocytes, and increases in AST. Grade 3 toxicities observed in more than 1 (12.5%) subject in any treatment group during the overall treatment phase were decreased WBC count, decreased neutrophil count, and increased GGT. Anemia and neutropenia were reported as AE in 1 (12.5%) subject from the Pbo/PR48 group each during the telaprevir/placebo treatment phase; laboratory abnormalities were not reported as AE in subjects dosed with telaprevir.
Cardiovascular Safety	Median changes from baseline in vital signs and ECG parameters were generally small and none of the changes were considered clinically relevant. Vital signs and ECG abnormalities were observed in at most 1 (12.5%) subject in any treatment group with telaprevir and none were reported as AE. None of the subjects had a QTcF value above 450 ms or a QTcF increase versus baseline of more than 60 ms.

Conclusions

The results of the present trial indicate that the in vivo intrinsic activity of telaprevir monotherapy against HCV genotype 4 is modest after 2 weeks of treatment and lower than that previously observed against HCV genotype 1 (trial VX04-950-101). The magnitude of HCV RNA decline at Day 15 observed in subjects receiving telaprevir and Peg-IFN-alfa-2a/RBV compared to that of telaprevir monotherapy and Peg-IFN-alfa-2a/RBV therapy, respectively, suggest synergy between these drugs against HCV genotype 4.

The difference between HCV genotypes 1 and 4 cannot be attributed to differences in exposure to telaprevir, which was consistent with previous trials. After 2 weeks of treatment, coadministration of telaprevir at 750 mg q8h, Peg-IFN-alfa-2a at 180 µg once-weekly, and RBV at 1,000-1,200 mg/day resulted in higher plasma concentrations of telaprevir compared to telaprevir monotherapy. Based on the LSmean ratios, telaprevir AUC_{8h} on Day 15 was 33% higher in the combination treatment compared to telaprevir monotherapy. Based on the ratios of the LSmeans, telaprevir AUC_{8h} on Day 1 was similar in the combination treatment and telaprevir monotherapy.

Previously characterized HCV genotype 1 amino acid substitutions associated with reduced susceptibility to telaprevir were detected in 4 subjects during telaprevir treatment (all were T54A/T mutations). These subjects achieved SVR24 with continued or subsequent Peg-IFN-alfa-2a/RBV treatment thus, suggesting that variants with reduced susceptibility to telaprevir remained sensitive to Peg-IFN-alfa-2a/RBV.

Telaprevir was generally well tolerated. The most frequent AEs during telaprevir treatment were influenza-like illness and asthenia.

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