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-C209 **Clinical Phase**: IIa
Title: A Phase IIa randomized, partially blinded trial of telaprevir (VX-950) in treatment-naïve subjects with chronic genotype 2 or 3 hepatitis C infection	
Investigator: [redacted] M.D., Barts and the London NHS Trust, 2 Newark Street, [redacted] United Kingdom	**Countries**: France, United Kingdom, Italy, Sweden
Trial Period: Start: 6-Dec-2007 End: 28-May-2009	**No. of Investigators**: 12 **No. of Subjects**: genotype 2: 23, genotype 3: 26

Objectives: The objectives of the trial were:

- to assess the effect of telaprevir (TVR) on genotype 2 and 3 hepatitis C virus (HCV) early viral kinetics, when administered over 2 weeks, alone or in combination with pegylated interferon (Peg-IFN)-alfa-2a and ribavirin (RBV);
- to evaluate the single-dose and steady-state pharmacokinetics of TVR and VRT-127394 (*R*-diastereomer of TVR), and the pharmacokinetic/pharmacodynamic relationship of TVR in subjects chronically infected with genotype 2 or 3 HCV;
- to assess and characterize pheno- and genotypically viral variants potentially arising during the entire course of the trial in treatment-naïve subjects treated with TVR with or without Peg-IFN-alfa-2a and RBV;
- to evaluate the safety and tolerability of 2-week treatment with TVR with or without Peg-IFN-alfa-2a and RBV in treatment-naïve subjects chronically infected with genotype 2 or 3 HCV.

Design: This was a Phase IIa multicenter, partially blinded, randomized, stratified for genotype, multiple-dose trial to assess the effect of TVR on HCV early viral kinetics in treatment-naïve subjects chronically infected with genotype 2 or 3 HCV.

A total of 48 subjects who had never been treated for their HCV infection, i.e., 24 subjects infected with HCV genotype 2 and 24 subjects infected with HCV genotype 3, were planned to be enrolled in the trial. The subjects were randomized in a 1:1:1 ratio to 1 of 3 investigational treatment groups. Randomization was stratified for genotype:

- Group A: TVR 750 mg every 8 hours (q8h)
  (N = 16; 8 subjects genotype 2 and 8 subjects genotype 3);
- Group B: TVR 750 mg q8h + Peg-IFN-alfa-2a 180 µg once-weekly + RBV 400 mg twice daily (b.i.d.)
  (N = 16; 8 subjects genotype 2 and 8 subjects genotype 3);
- Group C: Placebo q8h + Peg-IFN-alfa-2a 180 µg once-weekly + RBV 400 mg b.i.d.
  (N = 16; 8 subjects genotype 2 and 8 subjects genotype 3).

The trial consisted of a screening period lasting up to a maximum of 6 weeks, a treatment period of 24 (Groups B and C) or 26 (Group A) weeks, and a follow-up period of at least 24 weeks (and maximum 48 weeks). The treatment period consisted of a 2-week investigational treatment phase and a 22- or 24-week standard treatment phase.

All subjects received the investigational treatment regimen to which they had been randomized for 2 weeks. Subjects in Group A subsequently received 24 weeks of standard treatment (i.e., until Week 26) consisting of Peg-IFN-alfa-2a 180 µg once-weekly and RBV 400 mg b.i.d. Subjects in Groups B and C already received standard treatment during the investigational treatment phase and continued standard treatment until they had received 24 weeks of standard treatment in total.

After the end of treatment (EOT; i.e., either having completed the 24- [Groups B and C] or 26-week [Group A] treatment period or having discontinued all study medication earlier), all subjects were followed for at least 24 weeks in order to assess sustained virologic response (SVR) or to collect samples for viral sequencing. 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 of HCV RNA).

HCV 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, 18-65 years of age, inclusive.
2. Subjects chronically infected with either
   a) genotype 2 HCV with HCV RNA > 10,000 IU/mL, or
   b) genotype 3 HCV with HCV RNA > 10,000 IU/mL.

   Chronic disease status had to be confirmed by at least one 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 HCV infection was met, or
   - diagnosis of hepatitis C infection was to be made > 6 months before the screening period.
3. Subject who had never received treatment for HCV (including investigational products).
4. Screening laboratory values of the following variables had to meet the acceptable values: absolute neutrophil count ≥ 1,500/mm^3, platelet count ≥ 100,000/mm^3, and hemoglobin within normal range. All other hematology and biochemistry results had to show no clinically significant abnormalities in the opinion of the investigator.
5. Subjects judged to be in good health, in the opinion of the investigator, 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.
6. If heterosexually active, female subjects of childbearing potential had to agree to the use of two effective methods of contraception from screening until 4 months after the last dose of RBV, as outlined in Section 3.2.4. If heterosexually active, non-vasectomized male subjects who had a female partner of childbearing potential had to agree to the use of two effective methods of contraception from screening until 7 months after the last dose of RBV, as outlined in Section 3.2.4.
   Note: Hormonal contraceptives might not be reliable when taking TVR. Therefore, in order to be eligible for this trial, female subjects had to use 2 barrier methods during TVR/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 might cause the condoms to break). As of 1 month after completion of TVR/placebo treatment, hormonal contraceptives could be used as 1 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 post-menopausal for at least 2 years.
7. Subject was willing to refrain from the concomitant use of any medications or substances noted in Section 3.3.6.
8. Subject had 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 that 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 interferon (Peg-IFN-alfa-2a in particular) or RBV treatment, including but not limited to the following:
   - 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 history or evidence of decompensated liver disease as shown by screening laboratory results of any of the following:
   a. international normalized ratio (INR) ≥ 1.7;
   b. serum albumin < 3.5 g/dL;
   c. serum total bilirubin > 1.8 times the upper limit of normal (ULN), unless isolated and for subjects with Gilbert's syndrome;
   d. history of ascites, hepatic encephalopathy, bleeding esophageal varices.
4. Subject had 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 study procedures.
5. Subject had human immunodeficiency virus or hepatitis B virus co-infection.
6. Women who were pregnant, planning to become pregnant or breastfeeding, and partners of women who were pregnant or breastfeeding.
7. Subject had hypersensitivity to tartrazine.
8. 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 studies in the last 12 months.
9. Subject had history or evidence of cirrhosis.
10. Subject had any evidence of significant liver disease in addition to hepatitis C infection, which could include but was not limited to hepatitis B infection, drug or alcohol-related cirrhosis, autoimmune hepatitis, hemochromatosis, Wilson's disease, Nonalcoholic Steatohepatitis (NASH), or primary biliary cirrhosis.
11. Subject was diagnosed with or had suspected hepatocellular carcinoma. Alpha-fetoprotein at screening had to be < 50 ng/mL, or, if higher, absence of a mass on an ultrasound or magnetic resonance imaging (MRI) needed to be documented within the screening period.

Treatment	Telaprevir	Placebo	Peg-IFN-alfa-2a (Pegasys®)	Ribavirin (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	3057618R, 3060433R	3057587R, 3061197R	B0099, B1082	78914
Dose Regimen	Subjects were randomized to 1 of 3 investigational treatment groups (treatment labels are mentioned between brackets): <u>Group A (T2&PR24)</u>: Day 1 to 15: TVR 750 mg q8h; Day 15 to Week 26: Peg-IFN-alfa-2a 180 µg once-weekly and RBV 400 mg b.i.d. <u>Group B (T2/PR24)</u>: Day 1 to 15: TVR 750 mg q8h; Day 1 to Week 24: Peg-IFN-alfa-2a 180 µg once-weekly and RBV 400 mg b.i.d. <u>Group C (Pbo/PR24)</u>: Day 1 to 15: Placebo q8h; Day 1 to Week 24: Peg-IFN-alfa-2a 180 µg once-weekly and RBV 400 mg b.i.d. Randomization was stratified for HCV genotype to ensure balanced treatment allocation.			
Duration of Treatment	Investigational treatment for 2 weeks, followed by standard treatment for 24 weeks (T2&PR24) or 22 weeks (T2/PR24 and Pbo/PR24). All subjects thus received standard treatment for a total duration of 24 weeks.			
Duration of Trial	Screening: maximum 6 weeks; Treatment: 26 (T2&PR24) or 24 (T2/PR24 and Pbo/PR24) weeks; Follow-up: at least 24 weeks (and maximum 48 weeks).			
Disallowed Medication	Because the interaction potential of TVR 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 medication concomitantly with Peg-IFN-alfa-2a and RBV treatment, the package inserts of Peg-IFN-alfa-2a (Pegasys®) and RBV (Copegus®) were to be consulted.
Assessments	
Antiviral Activity	Plasma samples for HCV RNA quantification were obtained at every study visit, except at follow-up (FU) Week 26. During the investigational treatment phase, intensive sampling for the quantification of HCV RNA (viral kinetics) was performed, i.e., at several time points on Days 1 and 2, and predose on Days 3, 4, 8, 12, and 15.
Viral Sequencing	Sequencing analyses were performed on baseline and at breakthrough/relapse (variable time points) on samples with HCV RNA values 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 FU Week 26, and were analyzed upon request of the protocol virologist.
Pharmacokinetics	During the investigational treatment phase, intensive blood sampling for determination of TVR and VRT-127394 plasma concentrations was performed in all treatment groups, i.e., at several time points on Days 1, 2, and 15, and predose on Days 3, 4, 8, and 12. Blood samples for determination of Peg-IFN-alfa-2a serum and RBV plasma concentrations were taken in the T2/PR24 and Pbo/PR24 groups only, on Days 1, 2 (predose and 6h after intake), 3, 4, 8, and 15.
Safety	
Adverse Events	AEs were recorded at every visit up to and including the FU Week 4 visit. After the FU 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 biochemistry measurements were taken at screening, on Days 1, 4, 8, and 15, at Weeks 4, 6, and 14, at EOT, at FU Weeks 4, 12, and 24, and (in case of relapse) 24 weeks after relapse. - Urine samples for urinalysis were taken at screening, on Days 1, 2, 3, 4, 8, and 15, at Weeks 4, 6, and 14, at EOT, and at FU Week 4.
Cardiovascular Safety	- Vital signs (pulse rate, systolic and diastolic blood pressure) were measured at screening, on Days 1, 8, and 15, at Weeks 4 and 14, at EOT, and at FU Week 4. - Standard 12-lead ECGs were taken at screening, at Day 1 (predose and 3-5h postdose), and at Day 15 (at any time of the day).
Physical examination	A physical examination was performed at screening (including an eye examination), on Days 1 and 15, at Week 14, at EOT, and at FU Week 4.
Statistical Methods	All analyses were performed on the full analysis (FA) set, defined as all randomized subjects who received at least 1 dose of TVR or placebo. Demographic data and baseline characteristics were tabulated. The primary efficacy endpoint was to determine early viral kinetics by plasma HCV RNA quantification, which has been widely used in the evaluation of the primary efficacy in the clinical trials of HCV therapeutics. Secondary efficacy endpoints included virologic response, viral breakthrough, SVR, and relapse. Descriptive statistics were provided for continuous endpoints; categorical endpoints were tabulated. A longitudinal model was fitted to explore HCV RNA change. Virology analysis focused on detecting previously characterized genotype 1 associated TVR resistance-associated mutations (RAMs) in the NS3 region (i.e., V36A/M, T54A, R155K/T/I/M, and A156V/T/S) at baseline, viral breakthrough, or relapse. The incidence of individual mutations at baseline and at the above time points was tabulated. Further analyses aimed at identifying potential genotype 2/3-specific mutations selected when failing a TVR-containing regimen are pending.

Statistical Methods, Cont'd	Descriptive statistics were calculated for the plasma concentrations of TVR, Peg-IFN-alfa-2a, and RBV at each time point and included sample size (n), mean, 95% confidence interval, standard error (SE), standard deviation (SD), median, minimum and maximum. Descriptive statistics were also calculated for the derived pharmacokinetic parameters and additionally included geometric mean and 25% and 75% percentiles. Graphs of the mean plasma concentration-time profiles of TVR on Day 1 and 15 and of Peg-IFN-alfa-2a after the first dose were produced. Results of VRT-127394 are not discussed in this clinical research report, as it was decided that sufficient data on the pharmacokinetics of VRT-127394 had been obtained from previous studies and since VRT-127394 has a negligible contribution to efficacy. Pharmacokinetic-pharmacodynamic relationships for TVR with regards to both safety and efficacy were graphically explored. Safety data summaries were provided for adverse events, laboratory data, ECG, and vital signs.

Main Features of the Subject Sample and Summary of the Results

Subject Disposition - Baseline Characteristics	Genotype 2 infected subjects			Genotype 3 infected subjects		
	T2&PR24	T2/PR24	Pbo/PR24	T2&PR24	T2/PR24	Pbo/PR24
Number of subjects entered	9	5	9	8	9	9
(male/female)	(7/2)	(1/4)[a]	(5/4)	(5/3)	(8/1)	(9/0)
Age: median (range), years	42.0 (21-60)	59.0 (48-61)	52.0 (28-61)	43.0 (31-60)	44.0 (27-51)	39.0 (20-63)
BMI: median (range), kg/m^2	26.6 (19-33)	28.1 (20-36)	27.8 (24-37)	26.5 (23-36)	27.7 (20-36)	20.4[b] (17-30)
Discontinuations – reason						
AE	0	0	0	0	1	0
Subject lost to follow-up	2	0	0	1	0	3
Subject noncompliant	2	0	0	0	0	0

[a] Three additional subjects were randomized to this group but were not treated: 2 subjects withdrew consent prior to first intake and 1 subject stratified to genotype 2 was infected with HCV genotype 4.
[b] Data of only 8 subjects were available.

Antiviral Activity – Genotype 2	T2&PR24		T2/PR24		Pbo/PR24	
	N	Value	N	Value	N	Value
Log_{10} HCV RNA (IU/mL), median (range)						
Baseline actual value	9	6.61 (4.4; 7.3)	5	6.21 (5.3; 7.3)	9	6.15 (5.5; 7.4)
Change from baseline to Day 15	9	-3.66 (-5.4; -0.9)	5	-5.51 (-6.0; -4.6)	9	-4.83 (-6.0; -0.2)
Change from baseline to Week 24/26	7	-5.91 (-6.6; -3.7)	5	-5.51 (-6.6; -4.6)	9	-5.45 (-6.7; 0.7)
Virologic Response (HCV RNA < 10 IU/mL), n (%)						
by Day 15	9	0	5	2 (40.0)	9	2 (22.2)
by EOT	9	8 (88.9)	5	5 (100)	9	8 (88.9)
Median Time to Virologic Response (HCV RNA < 10 IU/mL), days	9	31.0	5	12.0	9	43.0
Cumulative Viral Breakthrough, n (%)						
by Day 15	9	6 (66.7)[a]	5	0	9	0
by Week 24/26	9	6 (66.7)[a]	5	0	9	1 (11.1)
Sustained Virologic Response, n (%)						
SVR12	9	6 (66.7)	5	5 (100)	9	8 (88.9)
SVR24	9	5 (55.6)[b]	5	5 (100)	9	8 (88.9)
Relapse, n (%)						
by FU Week 24	8	1 (12.5)	5	0	8	0

N = number of subjects with data; SVR12/24 = sustained virologic response 12 or 24 weeks after last actual dose
[a] Including 4 subjects with unconfirmed viral breakthrough during the investigational treatment phase
[b] One subject (CRF ID [redacted] was undetectable at FU Week 12 but was lost to follow-up by FU Week 24.

Antiviral Activity – Genotype 3	T2&PR24		T2/PR24		Pbo/PR24	
	N	Value	N	Value	N	Value
Log_{10} HCV RNA (IU/mL), median (range)						
Baseline actual value	8	6.65 (5.8; 7.1)	9	6.79 (5.4; 7.4)	9	6.92 (3.9; 7.3)
Change from baseline to Day 15	8	-0.54 (-1.0; -0.1)	9	-4.85 (-6.1; -2.3)	9	-4.72 (-6.1; -3.2)
Change from baseline to Week 24/26	8	-5.71 (-6.4; -0.9)	7	-5.50 (-6.7; -4.7)	9	-6.22 (-6.6; -3.2)
Virologic Response (HCV RNA < 10 IU/mL), n (%)						
by Day 15	8	0	9	2 (22.2)	9	1 (11.1)
by EOT	8	6 (75.0)	9	9 (100)	9	9 (100)
Median Time to Virologic Response (HCV RNA < 10 IU/mL), days	8	99.0	9	43.0	9	29.0
Cumulative Viral Breakthrough, n (%)						
by Day 15	8	3 (37.5)[a]	9	0	9	0
by Week 24/26	8	3 (37.5)[a]	9	0	9	0
Sustained Virologic Response, n (%)						
SVR12	8	4 (50.0)	9	6 (66.7)	9	4 (44.4)[b]
SVR24	8	4 (50.0)	9	6 (66.7)	9	4 (44.4)[b]
Relapse, n (%)						
by FU Week 24	6	2 (33.3)	9	3 (33.3)	9	2 (22.2)[c]

N = number of subjects with data; SVR12/24 = sustained virologic response 12 or 24 weeks after last actual dose

[a] Including 2 subjects with unconfirmed viral breakthrough during the investigational treatment phase

[b] Note that 2 additional subjects in the Pbo/PR24 group were undetectable at EOT and at at least 1 of the FU visits but were lost to follow-up by FU Week 12.

[c] Note that 1 additional subject in the Pbo/PR24 group was undetectable at EOT but had no HCV RNA measurements during follow-up due to being lost to follow-up.

Virology

The current analysis focused on the TVR RAMs previously observed in TVR studies involving genotype 1 infected subjects (V36A/M, T54A, R155K/T/I/M, and A156V/T/S).

No genotype 2 or 3 infected subjects had a previously observed TVR RAM at baseline.

In TVR-treated genotype 2 infected subjects, viral sequence analysis showed that TVR RAMs were detected in all 5 subjects with viral breakthrough who had viral sequence analysis available. Viral sequence analysis for the subject with relapse was only available for the FU Week 24 sample; no variants with TVR RAMs were found at this time point.

In TVR-treated genotype 3 infected subjects, variants carrying the previously characterized TVR RAM R155K mutation were detected in 2 of the 3 subjects with viral breakthrough. The subject with viral breakthrough and no TVR RAMs experienced viral relapse with a variant carrying the TVR RAM R155K mutation. A partial R155K/R mutation was detected for this subject at FU Week 24. No TVR RAMs were detected in the 3 other subjects for whom viral sequence analysis was available at the time of relapse.

Pharmacokinetics of telaprevir (mean ± SD, t_{max}: median [range])	**Genotype 2 infected subjects**		**Genotype 3 infected subjects**	
	T2&PR24	**T2/PR24**	**T2&PR24**	**T2/PR24**
Day 1				
n	9	5	7	8
C_{max}, ng/mL	1,886 ± 1,043	2,462 ± 761	1,497 ± 435	1,588 ± 1,090
t_{max}, h	3.0 (0.5-6.0)	4.0 (2.1-4.2)	4.0 (3.0-6.0)	4.0 (3.0-8.0)
AUC_{8h}, ng.h/mL	7,980 ± 4,658	11,248 ± 3,810	6,938 ± 1,828	6,979 ± 5,011
Day 15				
n	8	4	6	6
C_{0h}, ng/mL[a]	2,052 ± 1,374	3,117 ± 1,624	2,600	2,914 ± 427
C_{min}, ng/mL	1,605 ± 1,106	2,164 ± 1,398	1,800 ± 375	2,002 ± 659
C_{max}, ng/mL	3,261 ± 1,818	4,318 ± 1,518	2,898 ± 423	3,358 ± 377
t_{max}, h	3.6 (1.0-4.0)	3.0 (3.0-4.0)	2.5 (1.0-4.0)	3.0 (0.0-6.0)
AUC_{8h}, ng.h/mL	20,144 ± 11,129	26,588 ± 10,908	18,480 ± 3,011	20,895 ± 6,242
fluctuation index[b], %	67.68 ± 38.06	69.42 ± 42.21	48.39 ± 10.00	46.86 ± 22.93

[a] In genotype 2 infected subjects, n = 7 for T2&PR24 treatment and n = 3 for T2/PR24 treatment.
In genotype 3 infected subjects, n = 1 for T2&PR24 treatment and n = 5 for T2/PR24 treatment.
[b] n = 5 for T2/PR24 treatment in genotype 3 infected subjects

Pharmacokinetics of RBV (mean ± SD)	**Genotype 2/3 infected subjects**	
	Pbo/PR24	**T2/PR24**
Day 15		
n	8	4
C_{0h}, ng/mL	1,055 ± 282	1,723 ± 714

Safety – Genotype 2 (n = number of subjects with data)	**TVR/Pbo Treatment Phase**			**Overall Treatment Phase**		
	T2&PR24 N = 9	**T2/PR24 N = 5**	**Pbo/PR24 N = 9**	**T2&PR24 N = 9**	**T2/PR24 N = 5**	**Pbo/PR24 N = 9**
Adverse Events						
Most frequently reported AEs[a], n (%)						
Pruritus SSC	4 (44.4)	4 (80.0)	1 (11.1)	4 (44.4)	4 (80.0)	4 (44.4)
Asthenia	4 (44.4)	2 (40.0)	3 (33.3)	4 (44.4)	3 (60.0)	5 (55.6)
Influenza-Like Illness	1 (11.1)	2 (40.0)	3 (33.3)	2 (22.2)	3 (60.0)	3 (33.3)
Nausea	1 (11.1)	3 (60.0)	1 (11.1)	1 (11.1)	3 (60.0)	2 (22.2)
Headache	1 (11.1)	1 (20.0)	3 (33.3)	2 (22.2)	2 (40.0)	4 (44.4)
Anorexia	0	2 (40.0)	0	0	3 (60.0)	1 (11.1)
n (%) with 1 or more AEs	6 (66.7)	4 (80.0)	8 (88.9)	9 (100)	4 (80.0)	9 (100)
n (%) of deaths	0	0	0	0	0	0
n (%) with 1 or more other SAEs	0	0	0	1 (11.1)	2 (40.0)	0
n (%) of permanent discontinuations of TVR/placebo due to 1 or more AEs	0	1 (20.0)	0	0	1 (20.0)	0
n (%) with 1 or more grade 3 AEs	0	1 (20.0)	0	1 (11.1)	1 (20.0)	1 (11.1)
n (%) with 1 or more AEs at least possibly related to TVR/placebo	5 (55.6)	4 (80.0)	7 (77.8)	6 (66.7)	4 (80.0)	7 (77.8)

For genotype 2 infected subjects, no deaths were reported and 4 subjects experienced one or more SAEs during the whole trial (including follow-up); all started after the investigational treatment phase. One subject in the T2/PR24 group permanently discontinued TVR due to an AE (grade 3 rash). In addition to the latter subject, 1 subject in the T2&PR24 group and 1 in the Pbo/PR24 group reported a grade 3 AE (neutropenia for both) during standard treatment. In the majority of subjects, 1 or more AEs were considered at least possibly related to TVR/placebo, Peg-IFN-alfa-2a, and/or RBV in the opinion of the investigator.

Clinical Laboratory Tests	During the investigational treatment phase, the most frequently observed (in more than 3 subjects in any group) treatment-emergent graded toxicities were neutrophils (decreased), WBCs (decreased), and uric acid (increased). In the overall treatment phase, additional treatment-emergent graded toxicities observed in more than 3 subjects in any group were decreases in lymphocytes and hemoglobin. Decreases of AST and ALT levels were observed in all treatment groups. During investigational treatment, emerging grade 3 laboratory toxicities were observed for neutrophils in 1 subject each in the T2&PR24 and Pbo/PR24 group. Laboratory abnormalities were reported as AEs in 2 subjects in the T2&PR24 group (neutropenia and hypokalemia), in 2 subjects in the T2/PR24 group (anemia and hemoglobin decreased), and in 1 subject in the Pbo/PR24 group (neutropenia). Except for anemia that started on Day 15, these AEs emerged during standard treatment. All were grade 1 or 2 in severity, except for neutropenia of grade 3 in 2 subjects. For subjects in the TVR treatment groups, these AEs were considered not or unlikely related to TVR by the investigator, except for hypokalemia (judged possibly related to TVR). No action towards study medication was taken for any of these events.
Cardiovascular Safety	Median changes in vital signs parameters were generally small and none were considered clinically relevant. One subject was observed with a grade 3 abnormality for diastolic blood pressure (DBP) in the T2&PR24 group. No clinically relevant changes over time were observed for ECG parameters. The incidence of ECG abnormalities was low. None of the subjects with HCV genotype 2 had absolute QTcF values above 480 ms. QTcF increases versus baseline of more than 60 ms occurred in 1 (11.1%) subject in the T2&PR24 group; the corresponding absolute value was within normal limits. None of the abnormalities in ECG parameters were reported as AE.

SSC = special search category, created to ensure that all related events were tabulated and analyzed
[a] in > 40.0% of subjects in any group

Safety – Genotype 3 (n = number of subjects with data)	**TVR/Pbo Treatment Phase**			**Overall Treatment Phase**		
	T2&PR24 N = 8	**T2/PR24 N = 9**	**Pbo/PR24 N = 9**	**T2&PR24 N = 8**	**T2/PR24 N = 9**	**Pbo/PR24 N = 9**
Adverse Events						
Most frequently reported AEs[a], n (%)						
Influenza-Like Illness	3 (37.5)	5 (55.6)	4 (44.4)	4 (50.0)	6 (66.7)	4 (44.4)
Pruritus SSC	3 (37.5)	1 (11.1)	1 (11.1)	6 (75.0)	3 (33.3)	3 (33.3)
Fatigue	1 (12.5)	4 (44.4)	1 (11.1)	1 (12.5)	4 (44.4)	2 (22.2)
Nausea	0	4 (44.4)	0	0	4 (44.4)	2 (22.2)
Cough	0	0	2 (22.2)	0	0	4 (44.4)
Rash SSC	1 (12.5)	3 (33.3)	0	3 (37.5)	4 (44.4)	1 (11.1)
n (%) with 1 or more AEs	7 (87.5)	9 (100)	8 (88.9)	8 (100)	9 (100)	9 (100)
n (%) of deaths	0	0	0	0	0	0
n (%) with 1 or more other SAEs	0	0	0	0	1 (11.1)	0
n (%) of permanent discontinuations of TVR/placebo due to 1 or more AEs	0	0	0	0	0	0
n (%) with 1 or more grade 3 AEs	0	0	0	0	1 (11.1)	1 (11.1)
n (%) with 1 or more AEs at least possibly related to TVR/placebo	5 (62.5)	7 (77.8)	5 (55.6)	5 (62.5)	7 (77.8)	5 (55.6)

For genotype 3 infected subjects, no deaths were reported and 2 subjects experienced one or more SAEs during the whole trial (including follow-up); all started after the investigational treatment phase. One subject in the T2/PR24 group permanently discontinued Peg-IFN-alfa-2a and RBV due to an AE (grade 2 rash) during standard treatment. One subject in the T2/PR24 group (pharyngolaryngeal pain and pneumonia) and 1 subject in the Pbo/PR24 group (neutropenia) experienced one or more grade 3 AEs during standard treatment. In the majority of subjects, the investigator judged one or more AEs as at least possibly related to TVR/placebo, Peg-IFN-alfa-2a, and/or RBV.	
Clinical Laboratory Tests	During the investigational treatment phase, the most frequently observed (in more than 3 subjects in any group) treatment-emergent graded toxicities were observed for neutrophils, WBCs, and hemoglobin (all decreased). In the overall treatment phase, additional treatment-emergent graded toxicities observed in more than 3 subjects in any group were uric acid (increased) and lymphocytes (decreased) as well as hypophosphatemia. Decreases of AST and ALT levels were observed in all treatment groups. During investigational treatment, emerging grade 3 laboratory toxicities were observed for eosinophils (in 1 subject in the T2&PR24 group) and neutrophils (in 1 subject in the Pbo/PR24 group). Laboratory abnormalities were reported as AEs in 1 subject in the T2&PR24 group (anemia), in 1 subject in the T2/PR24 group (neutropenia), and in 4 subjects in the Pbo/PR24 group (anemia, neutropenia, and hemoglobin decreased). Except for 1 subject with neutropenia in the Pbo/PR24 group, these AEs emerged during standard treatment. All were of severity grade 1 or 2, except for grade 3 neutropenia in 1 subject in the Pbo/PR24 group. For subjects in the TVR treatment groups, the AEs were considered not related to TVR by the investigator and no action towards study medication was taken for these events.
Cardiovascular Safety	Median changes in vital signs parameters were generally small and none were considered clinically relevant. None of the abnormalities in vital signs parameters were considered clinically relevant, except for 1 subject who was reported with hypotension. No clinically relevant changes over time were observed for ECG parameters. None of the QTcF absolute values were above 450 ms. One (11.1%) subject in the Pbo/PR24 group was observed with a QTcF increase versus baseline of more than 60 ms (111 ms). Apart from 1 subject in the Pbo/PR24 group who had sinus bradycardia, none of the abnormalities in ECG parameters were reported as AE.

SSC = special search category, created to ensure that all related events were tabulated and analyzed
[a] in > 40.0% of subjects in any group

Conclusions

The results of the monotherapy groups of this trial suggest that TVR has activity against genotype 2 HCV but shows limited activity against genotype 3 HCV. The activity against genotype 2 HCV was further enhanced by the combination with Peg-IFN-alfa-2a/RBV.

The difference in response between genotype 2 and genotype 3 infected subjects cannot be attributed to difference in TVR exposure, as this was comparable in both groups at Day 15.

Telaprevir was generally well-tolerated. The most common AEs during TVR treatment were pruritus, asthenia, and nausea in genotype 2 infected subjects and influenza-like illness, fatigue, and nausea in genotype 3 infected subjects.

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