SYNOPSIS

Study Identification and Protocol Summary

Company: Tibotec BVBA **Trade Name**:- **Indication**: Chronic hepatitis C infection	**Drug Substance**: VX-950 **Study no.**: VX-950-TiDP24-C216 **Clinical Phase**: 3
Title: A randomized, double-blind, placebo-controlled, Phase III trial of 2 regimens of telaprevir (with and without delayed start) combined with pegylated interferon alfa-2a (Pegasys®) and ribavirin (Copegus®) in subjects with chronic genotype 1 hepatitis C infection who failed prior pegylated interferon plus ribavirin treatment.	
Investigator: Stefan Zeuzem, M.D. University Hospital Johann Wolfgang Goethe University, Department of Internal Medicine I, Theodor-Stern-Kai, Building 11, 60590 Frankfurt, Germany	**Country**: international
Study Period: Start: 19-Sep-2008 End: 28-Jul-2010	**No. of Investigators**: 105 **No. of Subjects**: 662

Objectives: The primary objective was to demonstrate the superior efficacy of telaprevir in combination with pegylated interferon alfa-2a (Peg-IFN-alfa-2a) and ribavirin (RBV) compared to standard treatment in subjects with genotype 1 chronic hepatitis C infection who failed prior treatment with Peg-IFN plus RBV. The aim was to reach this primary objective separately for both strata of treatment failures: prior non-responders (defined as subjects who did not reach undetectable hepatitis C virus [HCV] ribonucleic acid [RNA] levels) or prior relapsers (defined as subjects with detectable HCV RNA during the follow-up period after previous undetectable HCV RNA at end of treatment). This was evaluated by comparing the proportion of subjects achieving sustained virologic response (SVR) who were treated with either of 2 regimens of telaprevir (with and without delayed start) combined with Peg-IFN-alfa-2a and RBV, versus the proportion of subjects achieving SVR who were treated with standard treatment (Peg-IFN-alfa-2a and RBV).
SVR is defined as having undetectable plasma HCV RNA levels 24 weeks after the last planned intake of study drug.

The secondary objectives were to evaluate the effect of delayed start of telaprevir on the efficacy (SVR and secondary parameters) of telaprevir in combination with Peg-IFN-alfa-2a and RBV; the efficacy of 2 telaprevir-based regimens versus standard treatment for the 2 subgroups within the prior non-responders, namely (1) the prior null-responders (defined as subjects who had <2-log drop in HCV RNA at Week 12 of previous therapy) and (2) the prior partial responders (defined as subjects who had ≥2-log drop in HCV RNA at Week 12 of previous therapy, but who never achieved undetectable HCV RNA levels while on treatment); safety and tolerability of telaprevir in combination with Peg-IFN-alfa-2a and RBV; sequence (amino acid) changes from baseline in the HCV NS3-4A protease domain; the pharmacokinetics of telaprevir, Peg-IFN-alfa-2a, and RBV, and the pharmacokinetic-pharmacodynamic relationship of telaprevir with virologic response, safety and tolerability parameters. The influence of covariates such as sex, age, and body weight on the pharmacokinetics of telaprevir were also studied.

Design: This was a randomized, double-blind, placebo-controlled Phase 3 study with telaprevir in subjects with genotype 1 chronic hepatitis C infection who failed prior treatment with pegylated interferon (Peg-IFN; Peg-IFN-alfa-2a or Peg-IFN-alfa-2b) plus ribavirin (RBV).

The study was designed to compare the efficacy, safety, and tolerability of 2 regimens of telaprevir (with and without delayed start (DS) of telaprevir) combined with Peg-IFN-alfa-2a and RBV versus standard treatment (Peg-IFN-alfa-2a and RBV). Telaprevir was administered at a dose of 750 mg every 8 hours (q8h) and Peg-IFN-alfa-2a and RBV at standard doses, i.e., 180 µg once weekly and 1000 or 1200 mg/day (weight-based), respectively.

The study consisted of a screening period of approximately 4 weeks, a 48-week treatment period, and 24-week follow-up period.

Subjects were eligible to enroll in the study if they
(1) had an undetectable hepatitis C virus (HCV) ribonucleic acid (RNA) level at the end of a prior course of

Peg-IFN/RBV therapy but did not achieve sustained virologic response (SVR) (prior relapsers), or
(2) never had an undetectable HCV RNA level during or at the end of a prior course of Peg-IFN/RBV therapy (prior non-responders).

Approximately 650 subjects (350 prior relapsers and 300 prior non-responders) were planned to be randomized in a 2:2:1 ratio to one of 3 treatment groups, all with a planned total treatment duration of 48 weeks:

- Treatment group A (260 subjects: 140 prior relapsers and 120 prior non-responders): telaprevir in combination with Peg-IFN-alfa-2a and RBV for 12 weeks; followed by placebo in combination with Peg-IFN-alfa-2a and RBV for 4 weeks; followed by Peg-IFN-alfa-2a and RBV for 32 weeks.

- Treatment group B (260 subjects: 140 prior relapsers and 120 prior non-responders): placebo in combination with Peg-IFN-alfa-2a and RBV for 4 weeks; followed by telaprevir in combination with Peg-IFN-alfa-2a and RBV for 12 weeks; followed by Peg-IFN-alfa-2a and RBV for 32 weeks.

- Treatment group C (control group, 130 subjects: 70 prior relapsers and 60 prior non-responders): placebo in combination with Peg-IFN-alfa-2a and RBV for 16 weeks; followed by Peg-IFN-alfa-2a and RBV for 32 weeks.

Randomization was stratified based on screening HCV RNA value (<800000 IU/mL or ≥800000 IU/mL) and on type of prior response (prior relapser or prior non-responder). Furthermore, for the stratum of prior non-responders, an additional stratification was for prior null-responsers or prior partial responders, defined as follows:
(1) subjects with <2-log drop in HCV RNA at Week 12 of prior therapy (null-responders) or
(2) subjects with ≥2-log drop in HCV RNA at Week 12 of prior therapy but who never achieved undetectable HCV RNA levels while on treatment (partial responders).
Enrollment was limited such that neither of these strata would represent more than 55% of the non-responder subpopulation.

After the end of treatment (Week 48 or having discontinued earlier), subjects were followed until 24 weeks after last planned dose in order to assess SVR in subjects with undetectable HCV RNA levels or to collect samples for viral sequencing in the case of detectable HCV RNA or relapse during follow-up.

Safety/tolerability assessments were performed and adverse events (AEs), regardless of severity, were collected until the Safety Follow-up Visit 4 weeks after last dose of study drug. Thereafter, AE reporting continued for serious adverse events (SAEs) and Events of Special Interest (ESIs) only. HCV RNA quantification was performed throughout the treatment and follow-up period. Sequencing analyses of the HCV NS3 protease domain were performed on all baseline samples, in case of virologic failure or relapse, and at specific time points. Pharmacokinetic sampling was performed at sites that had the technical capability to process pharmacokinetic samples, in order to evaluate the plasma concentrations of telaprevir and RBV and serum concentrations of Peg-IFN-alfa-2a. A pharmacokinetic substudy to assess the steady-state pharmacokinetic profile of telaprevir was conducted in a subset of subjects at selected sites.

After the end of the study, subjects who had been assigned to one of the telaprevir regimens could be asked to participate in a study to investigate the long-term sustainability of virologic response in subjects achieving SVR or to study the evolution of resistant variants in non-responding subjects (Study VX08-950-112).

Subjects from the control group who failed therapy were offered the possibility to enter an open-label study with a telaprevir-based regimen in light of the efficacy of a telaprevir-based regimen in this subject population (Study VX-950-TiDP24-C219).

Subject Selection
Inclusion Criteria

1. Subject was male or female, 18 to 70 years of age, inclusive.
2. Subject had genotype 1 chronic hepatitis C infection with HCV RNA level ≥1000 IU/mL. Genotype had to be confirmed during screening. Chronic infection status had to be confirmed by diagnosis of HCV >6 months before the screening period.
3. Subject failed at least 1 prior course of Peg-IFN/RBV therapy, defined as:
   - Subject had an undetectable HCV RNA level (by branched-chain DNA [bDNA], reverse transcription-polymerase chain reaction [RT-PCR], or transcription mediated amplification [TMA]-based assay) at the end (6 weeks or less after the last dose of medication) of a prior course of at least 42 weeks of Peg-IFN/RBV therapy but did not achieve SVR (relapser); or
   - Subject never had an undetectable HCV RNA level (by bDNA, RT-PCR, or TMA-based assay) during or

at the end of a prior course of at least 12 weeks of Peg-IFN/RBV therapy (null-responder and partial responder).

Subject had to have received 80% or more of the intended dose of Peg-IFN/RBV.

The following information related to the virologic response to the last course of Peg-IFN/RBV therapy (that qualified as an adequate course as defined above) had to be available in the medical records of the subject:

- start and end date of the previous treatment course;
- HCV RNA results at start of treatment (all subjects), at 12 weeks after start of treatment (null and partial responders), at end of treatment (all subjects), and during follow-up (relapsers);
  Note: the following time window was allowed for the Week 12 assessment time point: Week 11 to Week 16
- HCV RNA assay used and limit of detection.

4. Subject had to have received the last dose of Peg-IFN or RBV at least 12 weeks before the Screening visit.
5. Subject was judged to be in good health (besides HCV infection) 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. Subject had a liver biopsy within 18 months prior to the Screening visit and the biopsy report had to be available, or he/she had to agree to have a biopsy performed within the screening period.
   Note: If a biopsy more than 18 months prior to screening already demonstrated histological cirrhosis (Metavir F4; Ishak score ≥5), the biopsy did not need to be repeated if the biopsy report could be provided.
   Note: If a biopsy was performed >18 months but ≤21 months prior to screening, the biopsy did not need to be repeated if information supportive of the absence of progression of fibrosis since the time of the previous biopsy was provided by the investigator (e.g., recent fibrotest/fiboscan consistent with previous results) and if the biopsy report could be provided.
7. Subjects with cirrhosis had to have serum alpha-fetoprotein (AFP) ≤50 ng/mL and normal abdominal ultrasound. If AFP >50 ng/mL or ultrasound abnormal, subjects had to have a computed tomography (CT) scan or magnetic resonance imaging (MRI) scan to exclude hepatocellular carcinoma.
8. If heterosexually active, a female subject of childbearing potential and a non-vasectomized male subject who had a female partner of childbearing potential had to agree to the use of 2 effective methods of contraception from screening onwards until 6 months (female subject) or 7 months (male subject) after the last dose of RBV.
   Note: Hormonal contraceptives may not be reliable when taking telaprevir. Therefore, to be eligible for this study, subjects had to use 2 other effective birth control methods during telaprevir/placebo treatment and for 2 months after the last intake of telaprevir/placebo. As of 2 months after completion of telaprevir/placebo treatment, hormonal contraceptives could again be used as one of the 2 required effective methods of birth control.
   Note: The use of birth control methods did not apply if the male partners had been vasectomized minimally 1 month prior to screening or if the female partners had a bilateral oophorectomy, a total hysterectomy, or tubal ligation, or if they had been post-menopausal for at least 2 years.
9. Subject was willing and able to refrain from the concomitant use of any medications, substances, or foods noted under the prior and concomitant therapy section in the protocol, from 14 days prior to the first day of study medication dosing through the end of treatment.
10. Subject was able to read and understand, and was willing to sign the Informed Consent Form (ICF) voluntarily before first study-related activity and abide by the study restrictions.
11. Subjects had to agree not to participate in other clinical studies for the duration of his/her participation in this study.

Exclusion Criteria

1. Subject was a previous non-responder that was classified as a viral breakthrough case i.e., subject had an undetectable HCV RNA level (by bDNA, RT-PCR, or TMA-based assay) during prior course of Peg-IFN/RBV therapy but regained detectable HCV RNA before therapy ended.
2. Subject was infected with HCV genotype 1 exhibiting more than one subtype.
3. Subject had HCV genotype 1 and exhibited co-infection with any other genotype.
4. Subject discontinued prior course(s) of Peg-IFN/RBV therapy due to a tolerance issue instead of lack of response.

5. Subject had any contraindication to the administration of Peg-IFN-alfa-2a or RBV, including but not limited to any of the following:
   - hypersensitivity to Peg-IFN-alfa-2a, RBV, or any of their components;
   - hemoglobinopathies (including thalassemia major, sickle-cell disease);
   - history or clinical evidence of significant or unstable cardiac disease (e.g., angina, congestive heart failure, recent myocardial infarction, significant arrhythmia) and/or clinically significant ECG abnormalities;
   - abnormal thyroid function that could not be controlled effectively by medication;
   - poorly controlled diabetes mellitus as evidenced by hemoglobin A1c (HbA1c) ≥8.5% at Screening;
   - creatinine clearance ≤50 mL/min at Screening;
   - antinuclear antibody (ANA) titer ≥1:640 at Screening, evidence of autoimmune-mediated disease (e.g., Crohn's disease, ulcerative colitis, idiopathic thrombocytopenic purpura, systemic lupus erythematosus, autoimmune hemolytic anemia, scleroderma, severe psoriasis), and/or evidence of autoimmune hepatitis.
6. Subject had a pre-existing psychiatric condition that could interfere with the subject's participation in and completion of the study, including but not limited to:
   - severe depression or hospitalization for depression;
   - schizophrenia, bipolar illness, severe anxiety, or personality disorder;
   - a period of disability or impairment due to a psychiatric disease within the past 5 years.
7. Subject had history of decompensated liver disease: history of ascites, hepatic encephalopathy, or bleeding esophageal varices, and/or any of the following screening laboratory results:
   - International Normalized Ratio (INR) of ≥1.5;
   - Serum albumin <3.3 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.
8. Subject showed evidence of significant liver disease in addition to hepatitis C, including but not limited to, drug or alcohol-related cirrhosis, autoimmune hepatitis, hemochromatosis, Wilson's disease, Nonalcoholic Steatohepatitis (NASH), or primary biliary cirrhosis.
9. Subject had active malignant disease or history of malignant disease within the past 5 years (with the exception of treated basal cell carcinoma).
10. Subject had history of seizure disorders.
11. Subject had history of organ transplant that required chronic immunosuppression (Note: corneal, skin, and hair grafts are allowed).
12. Subject had a medical condition that required use of systemic corticosteroids (e.g. severe asthma, severe arthritis, or autoimmune conditions, organ transplantation, adrenal insufficiency, etc.).
13. Diabetic or hypertensive subject with clinically significant ocular exam findings, e.g., retinopathy, cotton wool spots, and optic nerve disorder.
14. Subject had history or other clinical evidence of chronic pulmonary disease associated with functional impairment.
15. Subject had hemophilia.
16. Subject had evidence of serious or severe bacterial or fungal infection(s), including active tuberculosis.
17. Subject had human immunodeficiency virus (HIV) or hepatitis B virus (HBV) co-infection.
18. Subject had a history of acute or chronic pancreatitis.
19. Suspicion existed of alcohol, barbiturate, amphetamine recreational or narcotic drug use, current or within 2 years prior to the Screening visit, that in the investigator's opinion would compromise the subject's safety and/or compliance with study procedures.
20. Subject or female partner was pregnant, planning to become pregnant, or breastfeeding.
21. Subject had hypersensitivity to tartrazine (yellow dye #5).
22. Subject had a grade 3 laboratory abnormality as defined by the grading scale for the severity of AEs in hepatitis C clinical studies, with the following exceptions:
    - Grade 3 elevations in transaminsases (alanine aminotransferase [ALT]; aspartate aminotransferase [AST]). However, ALT/AST levels at Screening could not exceed 10 times ULN.
    - Grade 3 elevations in gamma-glutamyltransferase (GGT). However, subjects with grade 3 GGT elevations were only allowed to enter the study if there was no evidence of current alcohol abuse and there were no other clinically relevant laboratory abnormalities, as judged by the investigator.

    OR

subject had screening laboratory values of the following variables that did not meet the acceptable values defined below:

Laboratory variable	Acceptable values
Absolute neutrophil count	≥1,200/mm^3
Platelet count	≥90,000/mm^3
Hemoglobin	≥12 g/dL for females ≥13 g/dL for males
Uric acid	Within normal range
Thyroid stimulating hormone (TSH)	Within normal range, or adequately controlled thyroid function on treatment

23. Subject previously participated in:
    - any investigational study including direct acting anti-HCV agents or protease inhibitors; any clinical study within 12 weeks before drug administration or participation in more than 2 studies in the last 12 months (exclusive of the current study).

Treatment	**Telaprevir**	**Peg-IFN-alfa-2a (Pegasys)**	**RBV (Copegus)**
Concentration Dosage Form Usage	375 mg tablet oral	180 µg solution injection	200 mg tablet oral
Batch Number	3064088R, 3066476R, 3064086R, 3064087R, 3060435R	B1082, B1091, B1097	99971, 92859, 98334, 100043
Dose Regimen	Subjects were randomized to one of 3 treatment groups: <u>T12/PR48 (Treatment group A):</u> telaprevir 750 mg q8h from Day 1 through Week 12; placebo q8h from Week 12 through Week 16; Peg-IFN-alfa-2a 180 µg/week from Day 1 through Week 48; RBV 1000 or 1200 mg/day[a] (twice daily regimen). <u>T12(DS)/PR48 (Treatment group B)</u>: placebo q8h from Day 1 through Week 4; telaprevir 750 mg q8h from Week 5 through Week 16; Peg-IFN-alfa-2a 180 µg/week from Day 1 through Week 48; RBV 1000 or 1200 mg/day[a] (twice daily regimen). <u>Pbo/PR48 (Treatment group C):</u> placebo q8h from Day 1 through Week 16; Peg-IFN-alfa-2a 180 µg/week from Day 1 through Week 48; RBV 1000 or 1200 mg/day[a] (twice daily regimen). [a] RBV dosing was weight-based: <75 kg = 1000 mg/day, ≥75 kg = 1200 mg/day.		
Duration of Treatment	All 3 treatment groups had a planned treatment duration of 48 weeks. In both telaprevir regimens, subjects were to receive 12 weeks of telaprevir, with or without delayed start in combination with 48 weeks of standard treatment. In the control group subjects received only standard treatment for 48 weeks.		
Duration of Study	Screening: approximately 4 weeks Treatment: 48 weeks Follow-up: at least 24 weeks after last planned dose		
Disallowed Medication	Because of the interaction potential of telaprevir with medications that are substrates, inhibitors, or inducers of cytochrome P450 (CYP) 3A4/5, 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	
Efficacy	Plasma samples for HCV RNA quantification were obtained at every study visit, except at Week 28. Plasma HCV RNA levels were measured using the COBAS TaqMan® HCV test (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 analysis (population sequencing) was typically conducted on all baseline samples and in case of virologic failure or relapse (variable time points), if HCV RNA levels were above the limit of detection of the sequencing assay (~ 1000 IU/mL). In addition, plasma samples for viral sequencing were taken for storage at all visits during the study, except at Week 28, and were analyzed upon request of the Protocol Virologist.
Pharmacokinetics	In a pharmacokinetic substudy conducted in a subset of subjects, steady-state pharmacokinetic profiles of telaprevir over an 8-hour period were obtained between 6 and 8 weeks after initiation of study drug. In the main study, blood samples for analysis of telaprevir, RBV, and Peg-IFN were collected at sites with the technical capability to process these samples. At Week 6 and Week 8, a predose sample and a sample anytime postdose was taken. Samples taken on Day 8, Weeks 2, 5, 12, and 16, and at time of discontinuation (only when due to an AE) were collected at random time points during the dosing interval.
Safety	
Adverse Events	All AEs, serious and non-serious, were collected continuously from signing of ICF onwards until the Safety Follow-up Visit 4 weeks after last intake of study drug. After the Safety Follow-up Visit, AE reporting continued for SAEs and ESIs, i.e., all grade 3 skin rash events (whether or not they met the criteria for an SAE), all skin reactions resulting in discontinuation of any or all study drug, and all skin rash events meeting the criteria for an SAE were considered ESIs, only.
Clinical Laboratory	- Blood samples for hematology, coagulation, and biochemistry were taken at Screening, at baseline, on Day 8, at Weeks 2, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 36, and 48, at time of early discontinuation, and at Follow-up Week 4. At Screening, on Day 1, at Weeks 12 and 24, and at the Safety Follow-up Visit, a sample was to be collected with the subject in a fasting state. - Urine samples for urinalysis were taken at Screening, baseline, Weeks 4, 8, 12, 24, 36, and 48, at time of early discontinuation, and at Follow-up Week 4.
Cardiovascular Safety	Vital signs (pulse rate, systolic and diastolic blood pressure) were measured at Screening, baseline, Weeks 4, 12, 24, and 48, at time of early discontinuation, 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 ECGs were taken at Screening, baseline (predose and 3 to 5 hours postdose) and at any given time point at Week 6 and Week 12. Additional monitoring of ECG could be done if, in the opinion of the investigator, this was clinically indicated.
Physical Examination	A physical examination was performed at Screening (including an eye examination), baseline, Weeks 4, 12, 24, and 48, at time of early discontinuation, and Follow-up Week 4.

Exploratory	
Patient Reported Outcome (PRO) and Assessment of Healthcare Utilization	- Questionnaires (including Total Fatigue Score from the Fatigue Severity Scale (FSS), EQ-5D, and work productivity Questionnaires) were self-administered by the subject at baseline, Weeks 2 (only the FSS questionnaire), 4, 12, 24, and 48, and at time of early discontinuation. - Healthcare utilization was assessed at each visit from the baseline visit onwards until the last Follow-up Visit.
PAXgene™ DNA/RNA	- On Day 1, a PAXgene™ DNA sample for the evaluation of drug disposition genes (metabolic enzymes and drug transporters) and human leukocyte antigen (HLA) haplotype was collected. In addition, IL28B genotype (rs12979860) was determined on the extracted DNA samples. - On Day 1, and at Weeks 4 and 8, a PAXgene™ RNA sample for assessment of the expression of interferon inducible genes (IIGs) in peripheral blood and an additional plasma sample for proteomics profiling was collected.
Proteomics profiling	On Day 1 (predose), at Week 4, and at Week 8, 1 additional plasma sample (tube) was collected for proteomics profiling.
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 study drug. In addition, as a sensitivity analysis, the primary analysis was repeated for the per protocol (PP) set, which is the FA set excluding all subjects with protocol deviations related to adherence to study medication (major), related to concomitant medication (major), related to selection criteria (major), or related to compliance towards stopping rules of study medication (major or minor). The primary (and final) analysis was conducted once all subjects had reached Week 72 (i.e., 24 weeks after last planned dose) or had discontinued earlier. Demographic data and baseline characteristics are descriptively presented and tabulated per treatment group.

Statistical Methods (continued)	The primary parameter was the proportion of subjects in each treatment group achieving sustained virologic response, defined as having undetectable plasma HCV RNA levels 24 weeks after the last planned dose of study drug ($SVR24_{planned}$). In the primary analysis, the $SVR24_{planned}$ rates in Treatment groups A and B were each compared to the $SVR24_{planned}$ rates in Treatment group C, separately for both types of treatment failures (prior non-responders and relapsers). This was done by means of a logistic regression model. The logistic regression model included the following factors: treatment, type of prior response (relapser, partial responder and null-responder) and their interaction, and baseline HCV RNA as a covariate. Appropriate contrasts were constructed to compare Treatments A and B versus C in the stratum of prior relapsers, and prior non-responders (combining null and partial responders) separately. Results are presented and interpreted in terms of *P* values for the odds ratios between Treatment A and C, and between Treatment B and C. The 95% confidence interval (CI) of the odds ratios are also shown, as well as the difference in proportion of response, together with the corresponding 95% CI. Adjustment of significance level for multiple comparisons (A versus C and B versus C) was carried out using the Hochberg procedure. Additionally, appropriate contrasts using the same logistic regression model described above was applied to compare Treatments A and B versus C overall across all types of treatment failures and within the subgroup of null-responders and the partial responders; for these comparisons no adjustment for multiple comparison was made. If Treatment groups A and B were superior to Treatment group C in a certain population, a secondary analysis was planned to estimate the difference in $SVR24_{planned}$ between Treatment A and Treatment B in the considered population. A non-inferiority testing of non-delayed (A) versus delayed (B) telaprevir start was conducted with a non-inferiority margin of 10% along with 95% confidence interval of the difference between A and B estimated from the logistic regression. Furthermore, if in the above logistic regression an appropriate contrast statement showed that the difference between A and B was not significant at the 10% level in the population of null-responders or partial responders separately, the difference between pooled telaprevir arms (Treatment groups A and B) and the control group in the considered populations were planned to be estimated and tested in the above model. A sensitivity analysis, Cochran-Mantel-Haenszel (CMH) test, was performed and the same logistic model as above was fitted for the imputed $SVR24_{planned}$ (SVR last observation carried forward [LOCF] for control). $SVR24_{planned}$ rates in all groups were tabulated. Secondary efficacy parameters were compared pairwise between Treatments A and B versus C for prior non-responders and relapsers separately. All secondary parameters, including virologic response (i.e., having undetectable HCV RNA) and relapse, were evaluated in the same way as $SVR24_{planned}$ by means of logistic regression models.

Statistical Methods (continued)	Descriptive statistics (number of subjects, mean, standard deviation, minimum, and maximum) for $\log_{10}$ HCV RNA and changes in $\log_{10}$ HCV RNA from baseline were tabulated by time point and treatment group. 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/S, R155I/K/M/T, and A156S/T/V) at baseline, virologic failure, or relapse. Further analyses aimed at identifying new amino acid substitutions associated with reduced susceptibility to telaprevir and selected when failing a telaprevir-containing regimen. The incidence of amino acid substitutions at baseline and at the above time points was tabulated/listed. In the pharmacokinetic substudy, descriptive statistics were calculated for the plasma concentrations of telaprevir at each time point and for the derived pharmacokinetic parameters. Plasma concentration -time data are graphically presented. Plasma concentration-time data were analyzed using standard non-compartmental methods as well as population pharmacokinetic modeling. Pharmacokinetic parameters were subjected to an exploratory graphical analysis including various transformations in order to get a general overview. In the main study, individual pharmacokinetic parameters of telaprevir were estimated by Bayesian feedback using a population pharmacokinetic model. Descriptive statistics were calculated for telaprevir pharmacokinetic parameters. The influence of covariates such as sex, age, and body weight, on the pharmacokinetics of telaprevir was evaluated. Safety data summaries were provided for AEs, laboratory data, ECG, vital signs, and physical examination. Note that laboratory toxicity grades were determined according to the Division of AIDS (DAIDS) Grading list (4-grade scale for most parameters). This grading scale differed from the grading scale used for AEs (Grading Scale for the Severity of Adverse Events in Hepatitis C Clinical Studies; 3-grade scale). Special Search Categories (SSCs) were created 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 predefined SSC, was counted but counted only once. Pharmacokinetic-pharmacodynamic relationships for telaprevir with regards to both safety and efficacy were evaluated based on individual estimates of the telaprevir pharmacokinetic parameters in the main study. A Data and Safety Monitoring Board (DSMB) was formed to monitor the safety of this study.

Main Features of the Subject Sample and Summary of the Results

Subject Disposition	Overall Population, FA set		
	T12/PR48	**T12(DS)/PR48**	**Pbo/PR48**
Number of subjects treated	266	264	132
Total number (%) of subjects who:			
- Completed the study	245 (92.1)	248 (93.9)	110 (83.3)
- Discontinued the study	21 (7.9)	16 (6.1)	22 (16.7)
Adverse event	1 (0.4)	2 (0.8)	2 (1.5)
Subject ineligible to continue the study	6 (2.3)	3 (1.1)	2 (1.5)
Subject lost to follow-up	6 (2.3)	4 (1.5)	4 (3.0)
Subject withdrew consent	8 (3.0)	7 (2.7)	13 (9.8)[a]
Other[b]	0	0	1 (0.8)
Total number (%) of subjects who:			
- Completed at least 1 study drug	215 (80.8)	226 (85.6)	88 (66.7)
- Completed all 3 study drugs	166 (62.4)	185 (70.1)	50 (37.9)
- Discontinued 1 or 2 study drugs	49 (18.4)	41 (15.5)	38 (28.8)
- Discontinued all 3 study drugs	51 (19.2)	38 (14.4)	44 (33.3)

[a] Including subjects in the placebo group who rolled over to the VX-950-TIDP24-C219 study. In order to maintain sponsor blinding, subjects meeting criteria for roll-over were unblinded by the independent HCV RNA monitor and discontinuation reason in the C216 study was noted as consent withdrawn.

[b] No further information available in clinical database.

Demographic and Baseline Characteristics	Overall Population, FA set		
	T12/PR48 N = 266	**T12(DS)/PR48 N = 264**	**Pbo/PR48 N = 132**
Baseline HCV RNA (IU/mL), n (%)			
<800000	28 (10.5)	30 (11.4)	18 (13.6)
≥800000	238 (89.5)	234 (88.6)	114 (86.4)
Prior Response Category, n (%)			
Prior relapsers	145 (54.5)	141 (53.4)	68 (51.5)
Prior non-responder	121 (45.5)	123 (46.6)	64 (48.5)
Prior null-responders	72 (27.1)	75 (28.4)	37 (28.0)
Prior partial responders	49 (18.4)	48 (18.2)	27 (20.5)
Sex, n (%)			
Female	83 (31.2)	75 (28.4)	44 (33.3)
Male	183 (68.8)	189 (71.6)	88 (66.7)
Race, n (%)			
Caucasian/White	246 (92.5)	252 (95.5)	117 (88.6)
Black	11 (4.1)	8 (3.0)	11 (8.3)
Oriental/Asian	6 (2.3)	2 (0.8)	3 (2.3)
Other	3 (1.1)	2 (0.8)	1 (0.8)
Age (years)			
Mean (SD)	50.7 (8.51)	51.0 (8.24)	49.9 (9.74)
Range	23-69	24-70	21-69
BMI (kg/m^2)			
Mean (SD)	27.6 (5.03)	27.2 (4.81)	27.4 (4.62)
Assessment of liver fibrosis (biopsy), n (%)			
No or minimal fibrosis	51 (19.2)	68 (25.8)	35 (26.5)
Portal fibrosis	83 (31.2)	71 (26.9)	38 (28.8)
Bridging fibrosis	60 (22.6)	58 (22.0)	29 (22.0)
Cirrhosis	72 (27.1)	67 (25.4)	30 (22.7)
HCV genotype (NS3), n (%)			
1a	136 (51.9)	149 (56.9)	67 (52.3)
1b	126 (48.1)	113 (43.1)	61 (47.7)

The demographic data and baseline disease characteristics were comparable across treatment groups. Demographic data and baseline disease characteristics were also comparable between the prior relapser and non-responder subpopulations, except for baseline HCV RNA level and severity of liver disease (data not shown in table above). The proportion of subjects with a baseline HCV RNA level ≥800000 IU/mL was higher in the prior non-responder population (94.5%) than in the prior relapser population (83.3%). The proportion of subjects diagnosed with cirrhosis was higher in the prior non-responder population (31.5%) than in the prior relapser population (20.3%). No or minimal fibrosis was seen in 16.9% and 28.8% of the subjects in the prior non-responder and prior relapser population, respectively. Bridging and portal fibrosis were seen with similar incidences across the subpopulations.

N: number of subjects with data; n: number of subjects with that observation; SD: standard deviation

Efficacy	**FA set**					
	T12/PR48 N = 266		**T12(DS)/PR48 N = 264**		**Pbo/PR48 N = 132**	
$SVR24_{planned}$	N	n (%)	N	n (%)	N	n (%)
prior relapsers	145	121 (83.4)	141	124 (87.9)	68	16 (23.5)
prior non-responders	121	50 (41.3)	123	51 (41.5)	64	6 (9.4)
prior null-responders	72	21 (29.2)	75	25 (33.3)	37	2 (5.4)
prior partial responders	49	29 (59.2)	48	26 (54.2)	27	4 (14.8)

This study met its primary objective which was to demonstrate the superior efficacy of telaprevir in combination with Peg-IFN-alfa-2a and RBV compared to standard treatment in subjects with genotype 1 chronic hepatitis C infection who failed prior treatment with Peg-IFN plus RBV.

The primary endpoint was the proportion of subjects in each treatment group achieving sustained virologic response ($SVR24_{planned}$), defined as having undetectable plasma HCV RNA levels 24 weeks after the last planned dose of study medication. The proportion of subjects achieving $SVR24_{planned}$ was statistically significantly higher in each of the telaprevir treatment groups (with and without delayed start) than in the placebo group for prior relapsers and prior non-responders separately (all *P* values <0.001).

$SVR24_{planned}$ rates were similar between the T12/PR48 and T12(DS)/PR48 groups for prior relapsers and prior non-responders. The difference in $SVR24_{planned}$ rates (T12/PR48 versus T12(DS)/PR48) with 95% CI as estimated in the logistic regression model was -4.3% (-12.6%, 3.9%) for prior relapsers and -0.4% (-13.6%, 12.9%) for prior non-responders. Given the small sample size and lack of statistical power for the secondary analysis of non-inferiority testing, the 95% CIs for the difference between T12/PR48 and T12(DS)/PR48 were wide with the lower limit of 95% CIs crossing the non-inferiority margin of -10%, indicating that non-inferiority for the telaprevir arm without delayed start was not established in this study.

For the 2 subgroups of prior non-responders (prior null-responders and prior partial responders), the proportion of subjects achieving $SVR24_{planned}$ was also statistically significantly higher in each of the telaprevir treatment groups than in the placebo group (all *P* values <0.001).

	T12/PR48		**T12(DS)/PR48**		**Pbo/PR48**	
Virologic response (undetectable HCV RNA) at Week 72[a]	N	n (%)	N	n (%)	N	n (%)
prior relapsers	145	120 (82.8)	141	124 (87.9)	68	15 (22.1)
prior non-responders	121	51 (42.1)	123	51 (41.5)	64	6 (9.4)
prior null-responders	72	21 (29.2)	75	25 (33.3)	37	2 (5.4)
prior partial responders	49	30 (61.2)	48	26 (54.2)	27	4 (14.8)
On-treatment virologic failure[b]	N	n (%)	N	n (%)	N	n (%)
prior relapsers	145	2 (1.4)	141	1 (0.7)	68	18 (26.5)
prior non-responders	121	50 (41.3)	123	44 (35.8)	64	50 (78.1)
prior null-responders	72	41 (56.9)	75	35 (46.7)	37	31 (83.8)
prior partial responders	49	9 (18.4)	48	9 (18.8)	27	19 (70.4)
Cumulative viral breakthrough at EOT[c]	N	n	N	n	N	n
prior relapsers	145	2 + 0	141	1 + 1	68	2 + 2
prior non-responders	121	17 + 26	123	15 + 28	64	5 + 2
prior null-responders	72	17 + 20	75	13 + 20	37	3 + 1
prior partial responders	49	0 + 6	48	2 + 8	27	2 + 1
Relapse Week 72[d]	N	n (%)	N	n (%)	N	n (%)
prior relapsers	135	10 (7.4)	138	9 (6.5)	46	30 (65.2)
prior non-responders	69	16 (23.2)	72	18 (25.0)	9	3 (33.3)
prior null-responders	30	8 (26.7)	36	9 (25.0)	5	3 (60.0)
prior partial responders	39	8 (20.5)	36	9 (25.0)	4	0

N: number of subjects with data; n: number of subjects with that observation; EOT: end of treatment

[a] proportion of subjects with undetectable HCV RNA in the visit window Week 68 to 78

[b] On-treatment virologic failure was defined as either discontinuation due to meeting a virologic stopping rule or detectable HCV RNA at EOT with viral breakthrough.

[c] In each column, the number of subjects with viral breakthrough emerging during the telaprevir treatment phase (during which subjects received treatment with telaprevir/placebo and Peg-IFN/RBV) is shown before the '+'-sign. After the '+'-sign, the number of subjects with viral breakthrough emerging after the telaprevir treatment phase and during the standard treatment phase is presented.

[d] Percentages calculated relative to the number of subjects with undetectable HCV RNA at planned EOT (N).

Virology

In the telaprevir groups, sequencing analyses of NS3•4A in all subjects at baseline and at subsequent time points in subjects in the telaprevir treatment groups who did not achieve an SVR suggest the following:

- Predominant baseline resistance to telaprevir is rare, and treatment response in these subjects suggests that the presence of telaprevir-resistant variants does not necessarily lead to treatment-failure.
- Among subjects not achieving SVR, no differences were noted in the type of emerging viral variants between the T12/PR48 and T12(DS)/PR48 arms.
- On-treatment virologic failure (18.3%, 97/530), including subjects who discontinued due to a virologic stopping rule and/or with viral breakthrough, was more frequent in prior null-responders and genotype 1a subjects.
    - Subjects who had virologic failure during the telaprevir/placebo treatment phase (8.9%; 47/530) had predominantly higher-level telaprevir-resistant variants, suggesting that in these subjects the T/PR regimen successfully inhibited wild-type (WT) and lower-level telaprevir-resistant variants.
    - Subjects who had virologic failure during the standard treatment phase (9.4%; 50/530) had either lower- or higher-level resistant variants, or WT virus.
- Relapse was generally associated with lower-level telaprevir-resistant variants or WT virus.
- All subjects who discontinued telaprevir treatment before week 4 failed treatment with WT, suggesting that a 4-week duration is not sufficient to fully inhibit WT virus.
- In 58% (60/104) of subjects with telaprevir-resistant variants at the post-nadir time point resistant variants were no longer detected by population sequence analysis at the end of the study (median follow-up time 46.4 weeks), suggesting that the distribution of viral variants may return to pre-treatment levels over time.

Telaprevir Pharmacokinetics (Substudy) Mean (SD)	**T12/PR48**	**T12(DS)/PR48**
n	16[a]	23[a]
C_{0h}, ng/mL	3698 ± 1517	2997 ± 1222
C_{8h}, ng/mL	3673 ± 1495	3104 ± 1320
C_{min}, ng/mL	2984 ± 1311	2533 ± 989.2
C_{max}, ng/mL	5087 ± 1577	4637 ± 1434
t_{max}, h	4.00 (1.50 - 6.00)	4.00 (1.17 - 7.98)
AUC_{8h}, ng.h/mL	33840 ± 11010	29390 ± 10330
$C_{ss,av}$, ng/mL	4226 ± 1366	3668 ± 1293
Fluctuation index(FI), %	52.56 ± 22.76	60.13 ± 18.07

SD: standard deviation

[a] n=25 n=15 for C_{8h}, AUC_{8h}, $C_{ss,av}$ and FI

[b] for C_{0h}, C_{max}, t_{max} and n= 24 for C_{min}

Telaprevir Population Pharmacokinetics Mean (SD)	**T12/PR48**	**T12(DS)/PR48**
n	88	103
C_{min}, ng/mL	3396 ± 1115	3296 ± 1031
AUC_{8h}, ng.h/mL	30370 ± 9113	29791 ± 8400

Telaprevir Population Pharmacokinetics based on the Pooled Telaprevir Arms by Subgroups		**Telaprevir AUC_{8h} (h*ng/mL) Mean (SD)**
Prior response	Relapser (n=102)	31143 (9287)
	Non-responder (n=89)	28814 (7884)
Sex	Female (n=54)	34283 (9741)
	Male (n=137)	28392 (7701)
HCV genotype (NS3)	1a (n=114)	28975 (7711)
	1b (n=74)	31694 (9980)
Cirrhosis	Yes (n=50)	28661 (8605)
	No (n=141)	30553 (8733)
Body weight	≤74.39 kg (n=49)	33837 (9476)
	>74.39 ≤83 kg (n=49)	31392 (10559)
	>83 ≤92.76 kg (n=46)	29459 (5818)
	≥92.76 kg (n=47)	25313 (5501)

Safety

No major differences in safety data between the prior relapser and non-responder subpopulations were noted during the telaprevir/placebo treatment phase and the overall treatment phase. Therefore, the safety data for the overall population are presented.

Telaprevir/placebo treatment phase (from first intake of study drug until last telaprevir/placebo intake + 1 day) (N = number of subjects with data)	**Overall population, FA set**			
	T12/PR48 N = 266	**T12(DS)/PR48 N = 264**	**Pooled T12/PR48 N = 530**	**Pbo/PR48 N = 132**
Adverse Events (AEs)				
Most frequently reported AEs by preferred term (i.e., in >25% of the subjects in the pooled T12/PR48 group), n (%)				
Fatigue	138 (51.9)	124 (47.0)	262 (49.4)	51 (38.6)
Pruritus	132 (49.6)	130 (49.2)	262 (49.4)	35 (26.5)
Headache	106 (39.8)	101 (38.3)	207 (39.1)	46 (34.8)
Rash	91 (34.2)	88 (33.3)	179 (33.8)	24 (18.2)
Influenza like illness	85 (32.0)	90 (34.1)	175 (33.0)	33 (25.0)
Nausea	89 (33.5)	80 (30.3)	169 (31.9)	31 (23.5)
Anemia	72 (27.1)	83 (31.4)	155 (29.2)	18 (13.6)
n (%) with 1 or more AEs	258 (97.0)	255 (96.6)	513 (96.8)	126 (95.5)
n (%) of deaths	0	0	0	1 (0.8)
n (%) with 1 or more other SAEs	18 (6.8)	17 (6.4)	35 (6.6)	4 (3.0)
n (%) leading to permanent discontinuation of telaprevir/placebo	39 (14.7)	29 (11.0)	68 (12.8)	4 (3.0)
n (%) with 1 or more grade 3 AEs	77 (28.9)	75 (28.4)	152 (28.7)	21 (15.9)
n (%) with 1 or more rash SSC events	135 (50.8)	137 (51.9)	272 (51.3)	36 (27.3)
n (%) with 1 or more pruritus SSC events	144 (54.1)	135 (51.1)	279 (52.6)	36 (27.3)
n (%) with 1 or more anemia SSC events	82 (30.8)	90 (34.1)	172 (32.5)	19 (14.4)
n (%) with 1 or more anorectal SSC events	72 (27.1)	54 (20.5)	126 (23.8)	8 (6.1)

Overall treatment phase (from first intake of study drug until last intake of study drug + 30 days) (N = number of subjects with data)	**Overall population, FA set**			
	T12/PR48 N = 266	**T12(DS)/PR48 N = 264**	**Pooled T12/PR48 N = 530**	**Pbo/PR48 N = 132**
Adverse Events (AEs)				
Most frequently reported AEs by preferred term (i.e., in >25% of the subjects in the pooled T12/PR48 group), n (%)				
Fatigue	145 (54.5)	131 (49.6)	276 (52.1)	53 (40.2)
Pruritus	138 (51.9)	132 (50.0)	270 (50.9)	36 (27.3)
Headache	112 (42.1)	109 (41.3)	221 (41.7)	49 (37.1)
Rash	99 (37.2)	95 (36.0)	194 (36.6)	25 (18.9)
Nausea	94 (35.3)	87 (33.0)	181 (34.2)	31 (23.5)
Influenza like illness	85 (32.0)	94 (35.6)	179 (33.8)	33 (25.0)
Anemia	79 (29.7)	94 (35.6)	173 (32.6)	20 (15.2)
Insomnia	68 (25.6)	84 (31.8)	152 (28.7)	34 (25.8)
Diarrhoea	66 (24.8)	69 (26.1)	135 (25.5)	18 (13.6)
n (%) with 1 or more AEs	260 (97.7)	260 (98.5)	520 (98.1)	126 (95.5)
n (%) of deaths	0	1 (0.4)	1 (0.2)	1 (0.8)
n (%) with 1 or more other SAEs	33 (12.4)	32 (12.1)	65 (12.3)	7 (5.3)
n (%) with 1 or more grade 3 AEs	98 (36.8)	96 (36.4)	194 (36.6)	29 (22.0)
n (%) leading to permanent discontinuation of RBV	25 (9.4)	20 (7.6)	45 (8.5)	8 (6.1)
n (%) leading to permanent discontinuation of Peg-IFN	22 (8.3)	19 (7.2)	41 (7.7)	8 (6.1)
n (%) with 1 or more rash SSC events	151 (56.8)	148 (56.1)	299 (56.4)	42 (31.8)
n (%) with 1 or more pruritus SSC events	150 (56.4)	137 (51.9)	287 (54.2)	37 (28.0)
n (%) with 1 or more anemia SSC events	91 (34.2)	102 (38.6)	193 (36.4)	23 (17.4)
n (%) with 1 or more anorectal SSC events	75 (28.2)	59 (22.3)	134 (25.3)	10 (7.6)

Summary of AEs

Three deaths occurred during the study. One subject (Pbo/PR48 group) died during the telaprevir/placebo treatment phase and 2 subjects died during the follow-up phase (1 subject in the T12(DS)/PR48 group and 1 subject in the Pbo/PR48 group). The subject in the T12(DS)/PR48 group died during follow-up due to an SAE reported during treatment with Peg-IFN-alfa-2a and RBV alone (lung neoplasm malignant considered possibly related to telaprevir/placebo by the investigator; reported onset 96 days after last intake of telaprevir). Both deaths in the Pbo/PR48 group resulted from SAEs considered not related to telaprevir/placebo by the investigator (acute respiratory distress syndrome and cholecystitis in one subject; coma in the other subject).

During the telaprevir/placebo treatment phase, the most frequently reported AEs (in >25% of the subjects in the pooled T12/PR48 group) were fatigue, pruritus, headache, rash, influenza-like illness, nausea, and anemia. A higher incidence (i.e., difference >5%) in the pooled T12/PR48 group than the Pbo/PR48 group was observed for pruritus, rash, anemia, fatigue, diarrhea, influenza-like illness, nausea, hemorroids, and anorectal discomfort.

The majority of AEs were grade 1 or 2 in severity. Grade 3 AEs (mainly anemia, neutropenia, and leukopenia) were more frequent in the pooled T12/PR48 group (28.7%) than in the Pbo/PR48 group (15.9%). Serious AEs and AEs leading to permanent discontinuation of telaprevir/placebo were also more frequent in the pooled T12/PR48 group (6.6% and 12.8%, respectively) than in the Pbo/PR48 group (each 3.0%).

Rash SSC, pruritus SSC, anemia SSC, and anorectal signs and symptoms SSC events were more frequently reported in the pooled T12/PR48 group than the Pbo/PR48 group. Most SSC events were grade 1 or 2 in severity. Apart from rash SSC events and anemia SSC events, SSC events that were serious or led to permanent discontinuation of telaprevir/placebo occurred in <1% of the subjects in the pooled T12/PR48 group.

Summary of AEs (continued)

Rash ESI events were reported in 5.3% of the subjects in the pooled T12/PR48 group and in no subjects in the Pbo/PR48 group.
Rash SSC events that were grade 3 in severity, or serious, or led to permanent discontinuation of telaprevir/placebo occurred in 3.2%, 0.9%, and 4.2% of the subjects in the pooled T12/PR48 group, respectively, and did not occur in any subjects in the Pbo/PR48 group. In total, 15 subjects in the pooled T/PR48 group and no subjects in the Pbo/PR48 group received systemic corticosteroids for the treatment of rash SSC events, 134 and 12 received topical corticosteroids, and 99 and 4 received systemic antihistamines.

In all treatment groups, a marked decrease in mean hemoglobin values was observed during the first 6 weeks of treatment, followed by a slower decrease towards the end of telaprevir/placebo treatment. Mean reticulocytes levels increased during the first 6 weeks in all treatment groups but the increase was more pronounced in the Pbo/PR48 group. Differences with the control group in hemoglobin and reticulocytes levels disappeared after end of telaprevir treatment.
A higher incidence of grade 3 or 4 decreases in hemoglobin was observed in the pooled T12/PR48 group compared to the Pbo/PR48 group (58.5% versus 29.8%).
Anemia SSC events that were were grade 3 in severity, or serious, or led to permanent discontinuation of telaprevir/placebo occurred in 6.4%, 1.9%, and 2.8% of the subjects in the pooled T12/PR48 group, respectively, and in 0.8%, 0.8%, and in no subjects in the Pbo/PR48 group, respectively. In total, 10 subjects in the pooled T12/PR48 group and no subjects in the Pbo/PR48 group received erythropoiesis -stimulating agents (ESAs) for the treatment of anemia SSC events and 38 and 1 received blood transfusions.

Incidences of AEs were comparable between the T12/PR48 and T12(DS)/PR48 treatment groups and between the prior relapser and prior non-responder populations.

During the overall treatment phase, only a small increase in incidence of all AEs was observed compared to the telaprevir/placebo phase in the 3 treatment groups.

Clinical Laboratory Tests

Relevant differences in changes over time between the telaprevir groups and the Pbo/PR48 group were observed for hemoglobin, reticulocytes, ALT, AST, direct, indirect, and total bilirubin, lymphocyte count, platelet count, total cholesterol, low-densitiy lipoprotein (LDL), uric acid, and potassium. Hemoglobin and reticulocytes changes over time are discussed above.

For ALT, and AST steep decreases compared to baseline were observed during the first week of treatment in the T12/PR48 group and during Week 4 in the T12(DS)/PR48 group. For direct, indirect, total bilirubin, and uric acid, steep increases were observed during the first week of treatment in the T12/PR48 group and during Week 4 in the T12(DS)/PR48 group. A decrease in potassium was observed during the first week of telaprevir treatment in both telaprevir groups. Mean lymphocyte count values decreased markedly during the first 6 weeks of treatment. A steep decrease in platelet count values was observed during the first week of treatment. Total cholesterol and LDL values increased during telaprevir treatment in both the T12/PR48 and T12(DS)/PR48 groups, but not in the Pbo/PR48 group. These changes were all more pronounced in the telaprevir groups than the Pbo/PR48 group. Mean levels for all these laboratory parameters in the telaprevir groups returned to similar levels as the Pbo/PR48 group after completion of telaprevir dosing. Apart from changes in hemoglobin discussed above, these changes in laboratory parameters were of minimal clinical significance. Incidences of grade 3 or 4 laboratory abnormalities and AEs related to these laboratory parameters were low, except for decreases in hemoglobin and decreases in in absolute lymphocyte count.

During the telaprevir/placebo treatment phase, the most frequently reported (in >20% of subjects in the pooled T12/PR48 group) graded treatment-emergent laboratory abnormalities (any grade) were hyperuricemia, hypophosphatemia, decreases in hemoglobin, platelet count, white blood cell (WBC) count, absolute lymphocyte count, neutrophils, and total neutrophil count, increases in total cholesterol, and hyperbilirubinemia.

A higher incidence (i.e., difference >10%) of graded laboratory abnormalities in the pooled T12/PR48 group than the Pbo/PR48 group was observed for hyperuricemia, decreases in hemoglobin, platelet count, absolute lymphocyte count, total neutrophil count, and increases in LDL calculated and total cholesterol.

Clinical Laboratory Tests (continued)

The most frequent (in >5% of subjects in the pooled T12/PR48 group) treatment emergent laboratory abnormalities of grade 3 or 4 were hyperuricemia and decreases in hemoglobin, absolute lymphocyte count, neutrophils, and WBC count. In addition to grade 3 or 4 decreases in hemoglobin, a higher incidence (i.e., difference >5%) of grade 3 or 4 laboratory abnormalities in the pooled T12/PR48 group than the Pbo/PR48 group was observed for decreases in absolute lymphocyte count (21.2% versus 9.2%) and hyperuricemia (7.0% versus 0.8%).

Laboratory abnormalities other than anemia reported as AEs in >5% of subjects in the pooled T12/PR48 group were leukopenia and neutropenia. The incidence of these AEs was similar in the pooled T12/PR48 group and Pbo/PR48 groups.

No major differences in laboratory safety data were observed between the T12/PR48 and T12(DS)/PR48 treatment groups and between the prior relapser and non-responder subpopulations.

Cardiovascular Safety

Mean changes from baseline in vital signs parameters were generally small. None of the mean changes were considered clinically relevant. All treatment-emergent abnormalities in vital signs during the telaprevir/placebo treatment phase were observed in <10% of the subjects in the pooled T12/PR48 group. All AEs related to vital signs abnormalities were reported in <2% of the subjects in the pooled T12/PR48 group.

Mean changes from baseline in ECG parameters were generally small. None of the mean changes were considered clinically relevant. Abnormal QTcF values or increased relative to baseline are shown below.

	T12/PR48 N = 266	**T12(DS)/PR48 N = 264**	**Pooled T12/PR48 N = 530**	**Pbo/PR48 N = 132**
QTc (Fridericia), n (%)				
]450 ms, 480 ms]	11 (4.2)	8 (3.1)	19 (3.6)	5 (3.8)
]480 ms, 500 ms]	2 (0.8)	2 (0.8)	4 (0.8)	1 (0.8)
More than 500 ms	1 (0.4)	2 (0.8)	3 (0.6)	0
Increase by 30-60 ms	31 (11.9)	29 (11.1)	60 (11.5)	12 (9.2)
Increase by >60 ms	11 (4.2)	10 (3.8)	21 (4.0)	6 (4.6)

The incidence of treatment-emergent increased QTcF values of >450 ms and QTcF increases versus baseline of >60 ms was comparable between the 3 treatment groups. Most of the QTcF increases versus baseline of >60 ms corresponded to QTcF values within normal limits. However, 3 (0.6%) subjects in the pooled T12/PR48 had a treatment-emergent QTcF value >500 ms. The QTcF values >500 ms in these 3 subjects all corresponded to QTcF increases of >60 ms versus baseline. One of these 3 subjects had a screening QTcF value of 489 ms and another of these subjects was receving only Peg-IFN and RBV at the time of the QTcF value >500 ms. None of these 3 subjects experienced ECG-related AEs. No QTcF values >500 ms were reported in the Pbo/PR48 group.

Adverse events related to ECG reported during the telaprevir/placebo treatment phase were reported in <2% of the subjects in the pooled T12/PR48 group.

No major differences in vital signs and ECG data were observed between the T12/PR48 and T12(DS)/PR48 treatment groups and between the prior relapser and non-responder subpopulations.

Fibrotest

An improvement in Fibrotest® results relative to baseline was observed in 36.2% of subjects in the pooled T/PR48 group and 30.1% of subjects in the Pbo/PR48 group. A worsening of Fibrotest® results relative to baseline was observed in 9.2% of subjects in the pooled T/PR48 group and 16.8% of subjects in the Pbo/PR48 group. There appeared to be no relation between $SVR24_{planned}$ and change in Fibrotest® results.

Pharmacokinetic/pharmacodynamic relationships

Telaprevir AUC was a significant predictor of $SVR24_{planned}$ (p=0.006) in a multivariable analysis taking into account baseline log_{10} HCV viral load, treatment group (T12/PR48 versus T12(DS)/PR48), HCV subtype (1a versus 1b), prior response category (relapse, null- or partial responder), and the interaction between treatment group and prior response, but was not a significant predictor of RVR in the same model (p=0.221). Viral breakthrough and relapse rates tended to decrease with increasing telaprevir pharmacokinetic parameters C_{0h} and AUC.

Exposure to telaprevir was comparable between subjects who experienced a rash SSC event versus those without rash SSC events. For hemoglobin toxicity, however, higher exposure to telaprevir was observed in subjects with grade 3 treatment-emergent hemoglobin toxicity compared to those with grade 1 or 2 toxicity. The subgroups without hemoglobin changes or with grade 4 changes are too small for comparison.

Conclusions

Results of this study demonstrated superior efficacy in the primary endpoint $SVR24_{planned}$ of telaprevir 750 mg q8h in combination with Peg-IFN-alfa-2a and RBV compared to standard treatment (Peg-IFN-alfa-2a and RBV) in subjects with genotype 1 chronic hepatitis C infection who failed prior treatment with Peg-IFN plus RBV. Superiority of telaprevir versus placebo in $SVR24_{planned}$ rates was shown consistently in each prior response category, including prior relapsers, prior null-responders, and prior partial responders and across a broad spectrum of subject characteristics. Relapse and on-treatment virologic failure were more frequent with standard treatment (Peg-IFN-alfa-2a and RBV) than with telaprevir in combination with Peg-IFN-alfa-2a and RBV. Delayed start of telaprevir relative to Peg-IFN-alfa-2a and RBV did not result in added clinical benefit relative to simultaneous start of telaprevir and Peg-IFN-alfa-2a/RBV.

No differences in telaprevir exposure were apparent between prior relapsers and prior non-responders, subjects with HCV genotype 1a, or 1b, or subjects with or without cirrhosis while exposure was lower in the higher body weight quartiles, and in men compared to women. The telaprevir AUC was a significant predictor of $SVR24_{planned}$. Viral breakthrough and relapse rates tended to decrease with increasing telaprevir pharmacokinetic parameters C_{0h} and AUC. Exposure to telaprevir was comparable between subjects with or without a rash SSC event while higher exposure to telaprevir was observed in subjects with grade 3 treatment-emergent hemoglobin toxicity compared to those with grade 1 or 2 toxicity.

The safety profile of telaprevir 750 mg q8h in combination with Peg-IFN-alfa-2a and RBV was similar across populations by prior response status (prior relapsers and prior non-responders) and regardless of whether or not start of telaprevir was delayed relative to start of Peg-IFN-alfa-2a and RBV. The addition of telaprevir to Peg-IFN-alfa-2a and RBV treatment was associated with a higher rate of rash and anemia but treatment discontinuation due to rash or anemia was infrequent. Management of anemia was mainly done by means of RBV dose reduction which did not have a negative impact on $SVR24_{planned}$ rate.

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