SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	INCIVO®
Name of Active Ingredient(s)	VX-950 (telaprevir)

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Status: Approved

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Prepared by: Janssen Infectious Diseases - Diagnostics BVBA

Protocol No.: VX-950HPC3008

Title of Study: Open-Label, Phase 3b Study to Determine Efficacy and Safety of Telaprevir, Pegylated-Interferon-alfa-2a and Ribavirin in Hepatitis C Virus Treatment-Naïve and Treatment-Experienced Subjects With Genotype 1 Chronic Hepatitis C and Human Immunodeficiency Virus Type 1 (HCV-1/HIV-1) Coinfection

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Study Center(s): 39 sites in 8 countries: Spain (9 sites), Brazil (6 sites), Great Britain (6 sites), Russia (5 sites), France (4 sites), Australia (4 sites), Poland (3 sites), and Sweden (2 sites)

Publication (Reference):

Representative publications of data from the interim analyses:

- Bertelsen K, Montes M, Horban A, Ortega Gonzalez E, Kakuda T, De Backer K. Efficacy, safety and pharmacokinetics of telaprevir, Peg-IFN-alfa-2a, and ribavirin in combination with darunavir/ritonavir-based HAART in HCV/HIV-1 co-infected patients (INSIGHT substudy). Abstract at the European AIDS Clinical Society meeting in Brussels, Belgium, Oct 2013.
- Montes M, Nelson M, Girard P-M, Sasadeusz J, Horban A, Grinsztejn B, Zakharova N, Falconer K, Dierynck I, Luo D, Ma Y-W, Witek J. Telaprevir combination therapy in treatment-naïve and –experienced patients co-infected with HCV/HIV (INSIGHT STUDY): Week 12 interim analysis. Abstract at the European AIDS Clinical Society meeting in Brussels, Belgium, Oct 2013.
- Montes M, Nelson M, Girard P-M, et al. Telaprevir combination therapy in treatment-naïve and –experienced patients co-infected with HCV/HIV. Abstract at the 64th Meeting of the American Association for the Study of Liver Diseases in Washington DC, USA, Nov 2013.

Study Period: 26 March 2012 (First Patient Visit) to 3 June 2014 (Last Observation in the Database)

Phase of Development: 3b

Objectives:

The primary objective of this study was to assess the antiviral efficacy of telaprevir, pegylated interferon (Peg-IFN)-alfa-2a, and ribavirin (RBV) in hepatitis C virus genotype 1 (HCV-1)/human immunodeficiency virus type 1 (HIV-1)-coinfected subjects as measured by sustained virologic response ($SVR12_{planned}$), defined as having plasma HCV ribonucleic acid (RNA) levels <25 IU/mL 12 weeks after the last planned dose of HCV study drugs.

The secondary objectives of the study were:

- to compare the SVR rate from this study to a historical control SVR rate derived from literature in HCV-1/HIV-1-coinfected subjects treated with Peg-IFN and RBV;
- to assess the antiviral efficacy of response-guided therapy of 12 weeks telaprevir plus 24 or 48 weeks of Peg-IFN-alfa-2a and RBV in HCV treatment-naïve subjects coinfected with HCV-1/HIV-1;
- to assess the antiviral efficacy of response-guided therapy of 12 weeks telaprevir plus 24 or 48 weeks of Peg-IFN-alfa-2a and RBV in HCV treatment-experienced prior relapser subjects coinfected with HCV-1/HIV-1;
- to assess the antiviral efficacy of 12 weeks telaprevir plus 48 weeks Peg-IFN-alfa-2a and RBV in HCV treatment-experienced prior partial responder or prior null responder subjects coinfected with HCV-1/HIV-1;
- to evaluate safety and tolerability of telaprevir in combination with Peg-IFN-alfa-2a and RBV and permitted HIV antiretrovirals (ARVs) as assessed by adverse events (AEs) (including rash and opportunistic infections), clinical laboratory results (including $CD4^+$ and $CD8^+$ counts), HIV-1 RNA assessments, 12-lead electrocardiogram (ECG), and vital signs;
- to evaluate the pharmacokinetics (PK) of telaprevir;
- to evaluate the relationship between telaprevir pharmacokinetics and safety and efficacy endpoints (PK/pharmacodynamics [PD]);
- to evaluate relapse rates and on-treatment virologic failure rates;
- to evaluate changes from baseline in the amino acid sequence of HCV NS3-4A protease;
- to evaluate HIV-1 virologic failure rates.

An exploratory objective was to evaluate the effect of interleukin (IL) 28B status on virologic response.

The primary hypothesis in this study was that telaprevir in combination with Peg-IFN-alfa-2a and RBV had an expected $SVR12_{planned}$ rate in the range of 30% to 70% in HCV treatment-naïve and treatment-experienced subjects coinfected with HCV-1/HIV-1.

Methodology:

This was an open-label, single-arm, multicenter, Phase 3b study in HCV treatment-naïve and treatment-experienced subjects coinfected with HCV-1/HIV-1 to determine the efficacy and safety of telaprevir given in combination with Peg-IFN-alfa-2a and RBV.

Subjects with HCV-1/HIV-1 coinfection who were HCV treatment-naïve or HCV treatment-experienced were to be enrolled. Subjects were to be taking one of the permitted highly-active antiretroviral therapy

(HAART) regimens for HIV continuously from ≥12 weeks before screening with no anticipated requirement for switching ARVs through Week 14 (except lamivudine [3TC] could be substituted for emtricitabine [FTC], or FTC for 3TC). The permitted HAART regimens were selected on the basis of use in HIV treatments and considerations of known and potential drug-drug interactions (DDIs) between telaprevir and HIV therapies. They included two nucleoside/nucleotide reverse transcriptase inhibitors (N[t]RTIs) in combination with efavirenz (EFV), ritonavir-boosted atazanavir (ATV/r), raltegravir (RAL), etravirine (ETR), or rilpivirine (RPV). The NRTIs used were to be either tenofovir disoproxil fumarate (TDF) or abacavir (ABC), each in combination with either 3TC or FTC. Enrollment of subjects on a 800/100 mg once-daily (qd) darunavir with low-dose ritonavir (DRV/r)-based HAART was initiated at selected sites; these subjects enrolled in the main study were also mandatorily enrolled in a VX-950HPC3008 DRV substudy in order to be closely monitored.

All subjects were to receive 12 weeks of treatment with telaprevir 750 mg every 8 hours (q8h) in combination with Peg-IFN-alfa-2a 180 µg/week and RBV 800 mg/day divided in 2 intakes, except for subjects receiving HAART based on EFV who were to receive 12 weeks of treatment with telaprevir 1125 mg q8h in combination with Peg-IFN-alfa-2a 180 µg/week and RBV 800 mg/day divided in 2 intakes. At Week 12, telaprevir dosing was to end and subjects were to continue on Peg-IFN-alfa-2a and RBV. The total HCV treatment duration in this study was 24 or 48 weeks depending on the subject's prior HCV treatment response, liver disease status, and individual on treatment virologic response in this study.

To minimize the risk to subjects who were not demonstrating adequate virologic response and for consistency with standard guidelines for the treatment of genotype 1 chronic hepatitis C, HCV RNA results were monitored to determine if HCV treatment modifications were to be made for individual subjects.

HCV RNA and HIV-1 RNA quantification was to be performed throughout the treatment period. HCV RNA quantification was also to be performed during the follow-up period. Sequencing analyses of the HCV NS3-4A protease were to be performed on all baseline samples and in the case of on-treatment virologic failure or relapse. Additionally, other samples could be analyzed upon request of the protocol virologist.

Safety/tolerability assessments were to be performed throughout the treatment and follow-up periods.

Sparse blood sampling was to be performed in all subjects to assess the plasma pharmacokinetics of telaprevir and selected HIV ARVs at predefined time points.

Apart from sparse pharmacokinetic sampling in the main study, a PK substudy was performed in a subset of subjects at selected sites, to obtain intensive PK profiles of telaprevir and selected HIV ARVs. Details on substudy design and assessments are described in a separate protocol.

A 12-week DRV substudy was performed at selected sites in up to 20 subjects who were on a 800/100 mg qd DRV/r-based HAART regimen in the main study. In order to be eligible for enrollment in the main study, these subjects on 800/100 mg qd DRV/r-based HAART regimen had to agree to also participate in the DRV substudy in order to be closely monitored, to evaluate the intensive PK profiles of telaprevir, DRV, and ritonavir, to evaluate total and unbound (free) concentrations of telaprevir and DRV, and to assess HCV RNA responses, maintenance of HIV-1 virologic control, and safety. Details on substudy design and assessments are described in a separate protocol. The results of the DRV substudy are reported in detail in separate Clinical Study Reports (CSRs) (primary [Week 4] analysis and final [Week 12] analysis) and are summarized in this synopsis.

In the main study, an interim analysis was performed once all subjects had completed Week 12 (or had discontinued earlier). The intention of this interim analysis was to evaluate efficacy, safety, and pharmacokinetics during the first 12 weeks of HCV treatment (end of the telaprevir treatment period). No CSR was written for this interim analysis but the results of the interim analysis were presented at the 2013

meeting of the American Association for the Study of Liver Diseases and at the October 2013 meeting of the European AIDS Clinical Society.

The primary analysis of the main study was conducted once all subjects had completed HCV treatment and the follow-up visit 12 weeks after last planned dose of HCV study drugs, or had discontinued earlier, to determine $SVR12_{planned}$. The final analysis was conducted once all subjects had completed HCV treatment and the follow-up visit 24 weeks after the last planned dose of the HCV study drugs, or had discontinued earlier. The purpose of this final analysis was to assess secondary parameters that could only be analyzed after completion of the study ($SVR24_{planned}$) and to provide results on parameters for which additional data became available after the cutoff date of the primary analysis (study termination, relapse, viral sequencing, serious adverse events [SAEs] occurring during the follow-up period, and pregnancy test results). The results described in this synopsis are predominantly those of the primary analysis. In addition, results of the final analysis are incorporated in this synopsis, alongside the results of the primary analysis. Whenever data of the final analysis are shown, this is clearly indicated. All other data described are based on the primary analysis.

The primary and final analyses were conducted on the full analysis (FA) set, defined as all subjects who received at least one dose of HCV study drugs.

Number of Subjects (planned and analyzed):

Approximately 150 subjects coinfected with HCV-1/HIV-1 were planned to be enrolled, ie, approximately 60 HCV treatment-naïve and 90 HCV treatment-experienced subjects. Within the group of HCV treatment-experienced subjects, approximately 30 prior relapsers were to be enrolled. The remainder of HCV treatment-experienced subjects were to be prior partial responders and prior null responders.

In total, 162 subjects received at least one dose of HCV study drugs (FA set), ie, 64 HCV treatment-naïve subjects and 98 HCV treatment-experienced subjects. The latter included 51 prior null responders, 29 prior relapsers, and 18 prior partial responders.

The PK substudy was planned to be performed in a subset of approximately 20 subjects. Six subjects were enrolled in the PK substudy.

The DRV substudy was planned to be performed in up to 20 subjects who were on a 800/100 mg qd DRV/r-based HAART regimen in the main study. A total of 17 subjects (8 HCV treatment-naïve and 9 HCV treatment-experienced subjects) were enrolled in the DRV substudy.

Diagnosis and Main Criteria for Inclusion:

Main inclusion criteria were as follows: subjects were to be men and women between 18 and 70 years of age (inclusive) with genotype 1 chronic HCV infection and HCV RNA level >1,000 IU/mL. Subjects were to have a diagnosis of HIV-1 infection >6 months before the screening visit and were to be taking one of the permitted HAART regimens for HIV continuously from ≥12 weeks before screening with no anticipated requirement for switching ARVs through Week 14 (except 3TC could be substituted for FTC or vice versa). Subjects were to have a $CD4^+$ count >300 cells/mm^3 at screening and no value <200 cells/mm^3 within 6 months of the screening visit. Subjects were to have HIV-1 RNA <50 copies/mL or HIV-1 RNA undetectable by a local HIV-1 RNA viral load test at least once within 6 months prior to the screening visit, and could not have HIV-1 RNA values >200 copies/mL or greater than the lower limit of detection for assays with a limit of 500 copies/mL within 6 months of the screening visit. Subjects were to have HIV-1 RNA <50 copies/mL as assessed by Roche Taqman HIV-1 RNA v2 at screening.

Test Product, Dose and Mode of Administration, Batch No.:

Telaprevir, 750 mg q8h (or 1125 mg q8h if the HAART regimen was EFV-based), formulated as a caplet-shaped yellow film-coated tablet for oral administration (F007) containing 375 mg of telaprevir (batch numbers: BEL4001, BJL3G01, and BKL5B00).

Commercially available supplies of Peg-IFN-alfa-2a and RBV were used:

- Peg-IFN-alfa-2a (Pegasys®), 180 µg/week, formulated as a 180-µg solution for subcutaneous injection in a prefilled syringe (batch numbers: B1191, B1255B11, B1299B03, B1303B08, B1291B02, B3002B01, B3003B05, and B1308B04);
- RBV(Copegus®), 800 mg/day divided in 2 intakes, formulated as a 200-mg film-coated tablet for oral administration (batch numbers: 134919, 134978, and 899764).

Reference Therapy, Dose and Mode of Administration, Batch No.: not applicable

Duration of Treatment:

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

All subjects were to receive 12 weeks of treatment with telaprevir in combination with Peg-IFN-alfa-2a and RBV. At Week 12, telaprevir dosing was to end and subjects were to continue on Peg-IFN-alfa-2a and RBV. The total HCV treatment duration in this study was 24 or 48 weeks depending on the subject's prior HCV treatment response, liver disease status, and individual on treatment virologic response in this study, as follows:

- HCV treatment-naïve subjects and prior relapsers who had extended rapid virologic response (eRVR; defined as having plasma HCV RNA '<25 IU/mL, target not detected' at Weeks 4 and 12 of HCV treatment) and did not have cirrhosis were to receive an additional 12 weeks of Peg-IFN/RBV alone (total treatment duration: 24 weeks);
- HCV treatment-naïve subjects and prior relapsers who did not achieve eRVR or who had cirrhosis (irrespective of HCV RNA at Weeks 4 or 12) were to receive an additional 36 weeks of Peg-IFN/RBV alone (total treatment duration: 48 weeks);
- All prior nonresponders (null or partial responders) irrespective of on-treatment virologic response or liver disease status were to receive an additional 36 weeks of Peg-IFN/RBV alone (total treatment duration: 48 weeks).

Criteria for Evaluation:

Antiviral Activity:

Blood samples for HCV RNA quantification were obtained at screening, on Day 1 predose (baseline), and at Weeks 4, 8, 12, 24, 36, and 48, or at time of discontinuation, and during follow-up. The sample at baseline was taken predose, whereas the other samples could be taken predose or postdose. Plasma HCV RNA values were measured using the High Pure System COBAS TaqMan HCV test (v2.0; lower limit of quantification [LLOQ] 25 IU/mL).

HCV Viral Sequencing:

Sequencing analyses of the HCV NS3-4A protease were performed on all baseline samples and in the case of on-treatment virologic failure or relapse. Additionally, other samples could be analyzed upon request of the protocol virologist.

Pharmacokinetics:

In the main study, sparse plasma samples were collected any time postdose at Weeks 2, 4, and 8 for the determination of telaprevir concentrations and at baseline (Day 1; predose) and any time postdose at Weeks 2, 4, 8, and 24 for the selected HIV ARVs ABC, ETR, RAL, DRV, and ritonavir. The samples from Week 24 were analyzed for DRV and ritonavir but not for ABC, ETR, and RAL. Note that also RPV was a selected HIVARV for sparse sampling but none of the subjects were on an RPV-based HAART regimen.

In the PK substudy, blood samples for intensive steady-state PK profiling of telaprevir and selected ARVs were collected predose (within 15 minutes before intake of telaprevir), and at 0.5, 1, 2, 2.5, 4, 6, and 8 hours after intake of telaprevir, at least 2 weeks and up to 4 weeks after initiation of study drug at selected sites. An additional blood sample at 10 hours after the morning intake of telaprevir was collected for subjects receiving EFV to determine EFV plasma concentrations. These assessments were specified in a separate protocol for this intensive PK substudy.

In the DRV substudy, samples to assess a full PK profile of DRV and ritonavir were to be collected on Day -1 and at Week 2 predose, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose, and samples to assess a full PK profile of telaprevir were to be collected at Week 2 predose, 0.5, 1, 2, 3, 4, 6, and 8 hours postdose. Sparse PK samples were to be collected to determine total telaprevir, DRV, and ritonavir plasma concentration at Week 1 any time postdose. An additional sample was to be collected to measure protein binding of DRV (Day -1 and Week 2) and telaprevir (Week 2).

Safety:

Adverse Events:

All AEs were collected continuously from signing of the informed consent form (ICF) onwards until the Safety Follow-up Visit, scheduled 4 weeks after the last intake of HCV study drugs. Thereafter, only SAEs (regardless of causality) were reported.

Clinical Laboratory Tests:

Samples for clinical laboratory tests were obtained at screening, on Day 1 predose (baseline), and at Weeks 1, 2, 4, 8, 12, 16, 24, 36, and 48, or at time of discontinuation, and at follow-up 4 weeks after the last dose of HCV study drugs. Additional laboratory testing could be performed in the event of rash. A midstream urine sample had to be collected for urinalysis by dipstick for protein, glucose, and occult blood at selected time points during the study. If urinalysis was abnormal, microscopic examination for white blood cells (WBC), red blood cells (RBC), and casts was performed.

HIV-1 RNA:

Blood samples for HIV-1 RNA quantification were obtained at screening, on Day 1 predose (baseline), and at Weeks 4, 8, 12, 24, 36, and 48, or at time of discontinuation, and during follow-up. Plasma HIV-1 RNA values were to be measured using the Roche Taqman HIV-1 RNA v2 test.

HIV viral sequencing was to be performed when HIV-1 RNA result was >200 copies/mL and a confirmatory HIV-1 RNA result >50 copies/mL was observed.

Electrocardiogram:

ECGs were recorded at screening, on Day 1 predose, and at Weeks 1, 2, 4, 8, and 16. Twelve-lead ECGs were recorded at a paper speed of 25 mm per second until 4 regular consecutive complexes were available.

Vital Signs:

Vital signs including systolic and diastolic blood pressure (SBP and DBP) and pulse rate were collected at screening, on Day 1 predose, at Weeks 2, 12, and 48, or at time of discontinuation, and at follow-up 4 weeks after the last dose of HCV study drugs.

Physical Examination:

A complete physical examination was performed at screening and at the follow-up visit 4 weeks after the last dose of HCV study drugs. At the other selected time points, a targeted physical examination was performed.

Pharmacogenomics:

If ABC was part of the HAART regimen, the subject was to have documented HLA-B*5701 negative results prior to screening. If no HLA-B*5701 result was available for a subject who was taking ABC as part of his/her HAART regimen, the HLA-B*5701 genotype was to be determined at screening.

A pharmacogenomic blood sample was to be collected at baseline to determine the subject's IL28B rs12979860 genotype and to explore the effect of the IL28B genotype on the subject's treatment outcome.

Statistical Methods:

An interim analysis was performed once all subjects had completed Week 12 (or had discontinued earlier). A primary analysis was conducted once all subjects had completed HCV treatment and the follow-up visit 12 weeks after last planned dose of HCV study drugs, or had discontinued earlier, to determine $SVR12_{planned}$. A final analysis was conducted once all subjects had completed HCV treatment and the follow-up visit 24 weeks after last planned dose of HCV study drugs, or had discontinued earlier.

The entire analysis was conducted on the FA set, defined as all subjects who received at least one dose of HCV study drugs.

Sample Size Determination:

The sample size was determined from the considerations of providing the estimation of SVR rate and the exact 95%, 2-sided CI with a proper precision as well as in comparison to the historical control SVR rate.

With the SVR rates ranging from 30% to 70%, the following table provides a range of sample sizes from 40 to 70 subjects and the associated 95% exact CI for the SVR rates.

Estimated Two-Sided 95% Exact Confidence Intervals for Different Sample Sizes and Response Rates

	SVR (%)				
Sample size	**30%**	**40%**	**50%**	**60%**	**70%**
40	(16.6%, 46.5%)	(24.9%, 56.7%)	(33.8%, 66.2%)	(43.3%, 75.1%)	(53.5%, 83.4%)
50	(17.9%, 44.6%)	(26.5%, 54.8%)	(35.5%, 64.5%)	(45.2%, 73.6%)	(55.4%, 82.1%)
60	(18.8%, 43.2%)	(27.6%, 53.5%)	(36.8%, 63.2%)	(46.5%, 72.4%)	(56.8%, 81.2%)
70	(19.6%, 42.1%)	(28.5%, 52.4%)	(37.8%, 62.2%)	(47.6%, 71.5%)	(57.9%, 80.4%)

With the expected SVR rates of 56% in HCV treatment-naïve subjects, 63% in prior relapse, and 35% in prior nonresponder populations, the following table provides a precision of the SVR estimates along with the exact 95% CI, given the sample size of approximately 60 subjects for HCV treatment-naïve subjects, approximately 30 subjects for prior relapsers, and approximately 60 subjects for prior nonresponders.

The expected SVR rates were based on the observed SVR rates from VX07-950-108 (Study 108) and VX-950-TiDP24-C216 (Study C216) in HCV-1 monoinfected subjects, with a scaling factor of 75% to take into consideration the special patient population of HIV/HCV-coinfection and the likelihood of decreased virologic response as compared to the HCV-1 monoinfected patients.

Study population	Sample Size	Expected SVR	Exact 95% CI
HCV treatment-naïve	60	56%	(43%, 69%)
Prior relapse	30	63%	(44%, 80%)
Nonresponder	60	35%	(23%, 48%)

The historical control SVR rate in HCV treatment-naïve subjects was based on Torriani FJ (2004), in which the end of follow-up (Week 72) SVR was reported as 29% (51/176) in genotype 1 HCV/HIV-coinfected subjects. Since there were no direct data on HCV/HIV-coinfected HCV treatment-experienced subjects, the SVR rates from the monoinfection studies (Study 108 and Study C216) on the control were utilized with a scaling factor of 75%.

Study population	Historical control SVR rate
HCV treatment-naïve	29%
Prior relapse	18%
Nonresponder	7%

Therefore, a sample size of approximately 60 HCV treatment-naïve, approximately 30 prior relapsers, and approximately 60 prior nonresponder subjects was considered adequate for the estimation of SVR, leading to a total sample size of 150 subjects.

Antiviral Activity:

The primary parameter was the proportion of subjects achieving $SVR12_{planned}$, defined as having plasma HCV RNA levels <25 IU/mL 12 weeks after the last planned dose of HCV study drugs. The primary analysis on the primary endpoint was conducted using a snapshot approach, where the SVR assessment was based on the last HCV RNA value using an LLOQ of 25 IU/mL in the Week 12 follow-up visit window. '$SVR12_{planned}$ (Snapshot)' is referred to as '$SVR12_{planned}$'for simplicity.

The secondary parameters related to antiviral activity were:

- Proportion of subjects achieving $SVR12_{planned}$ (Classic), defined as having plasma HCV RNA levels '<25 IU/mL, target not detected' at end of HCV treatment and up to 12 weeks after the last planned dose of HCV study drugs (ie, no confirmed detectable HCV RNA in between);
- Proportion of subjects achieving $SVR24_{planned}$ (Snapshot), defined as having plasma HCV RNA levels <25 IU/mL 24 weeks after the last planned dose of HCV study drug, based on the last HCV RNA value using an LLOQ of 25 IU/mL in the Week 24 follow-up visit window;
- Proportion of subjects achieving $SVR24_{planned}$ (Classic), defined as having plasma HCV RNA levels '<25 IU/mL, target not detected' at the end of HCV treatment and up to 24 weeks after the last planned dose of HCV study drug;
- Proportion of subjects with rapid virologic response (RVR), defined as having plasma HCV RNA '<25 IU/mL, target not detected' at Week 4 of HCV treatment;
- Proportion of subjects with eRVR, defined as having plasma HCV RNA or '<25 IU/mL, target not detected' at Weeks 4 and 12 of HCV treatment;
- Proportion of subjects having plasma HCV RNA <25 IU/mL or '<25 IU/mL, target not detected' at Week 12 of HCV treatment;
- Proportion of subjects having plasma HCV RNA <25 IU/mL or '<25 IU/mL, target not detected' at the actual end of HCV treatment (ie, Week 24, Week 48, or early discontinuation of HCV treatment);

- Proportion of subjects having plasma HCV RNA <25 IU/mL or '<25 IU/mL, target not detected' at the planned end of HCV treatment (ie, Week 24 or Week 48);
- Proportion of subjects with on-treatment virologic failure, ie, subject met a virologic stopping rule and/or met the definition of viral breakthrough (ie, having a confirmed increase >1 $\log_{10}$ in HCV RNA level from the lowest level reached during the considered treatment phase, or a confirmed value of HCV RNA >100 IU/mL in subjects whose HCV RNA had previously become <25 IU/mL [detected or target not detected] during the considered treatment phase);
- Proportion of subjects with viral breakthrough;
- Proportion of subjects who relapsed (Snapshot), defined as having confirmed detectable plasma HCV RNA from planned end of HCV treatment onwards (ie, Week 24 or Week 48) after previous HCV RNA <25 IU/mL at planned end of HCV treatment, and not achieving $SVR12_{planned}$ (Snapshot);
- Proportion of subjects who relapsed (Snapshot, target not detected); same definition as relapse (Snapshot) but with cutoff '<25 IU/mL, target not detected';
- Proportion of subjects who relapsed (Classic), defined as having confirmed detectable plasma HCV RNA between end of HCV treatment and the follow-up Week 12 time point after plasma HCV RNA '<25 IU/mL, target not detected' at actual end of HCV treatment;
- Change from baseline in log HCV RNA values at each time point during HCV treatment.

The exploratory objective was to evaluate the proportion of subjects with virologic response by IL28B genotype.

HCV Viral Sequencing:

Changes from baseline in the amino acid sequence of the HCV NS3 protease domain were evaluated in subjects who had on-treatment virologic failure or relapse. The results of HCV genotyping were evaluated by the protocol virologist. Relevant changes were tabulated and described. Changes in the HCV viral genotype were not regarded as AEs.

Reversion to wild-type (WT) or pretreatment state was presented descriptively.

Pharmacokinetics:

Population PK:

Measured telaprevir plasma concentration-time data from both the main study and intensive PK substudy were used to estimate PK parameters during the 12-week dosing period. Bayesian feedback analysis was performed using a previously developed telaprevir PK model. The model was a one compartment linear model with first-order absorption. The fixed effects parameters of the model were apparent volume of distribution (V/F), apparent clearance (CL/F), and a first-order absorption rate constant (KA).

Sparse Sampling for ARVs:

Data from sparse PK sampling for selected ARVs in the main study was not subjected to any data handling. Data were listed for all subjects with available plasma concentrations. Descriptive statistics were determined without dose normalization to provide a general indication of the plasma levels reached within the studied population.

Intensive PK Substudy:

Based on the individual plasma concentration-time data, using the actual sampling times, the following pharmacokinetic parameters were derived from the bioanalytical results: for telaprevir and HIV ARVs: Week 4: maximum observed plasma concentration (C_{max}), time to reach the maximum observed plasma concentration (t_{max}), the observed plasma concentration just prior to the start of a dosing interval (C_{trough}), plasma concentration 8 hours after dosing (C_{8h}), minimum observed plasma concentration (C_{min}), area under the plasma concentration-time curve from time of administration to 8 hours after dosing (AUC_{8h}), average steady-state plasma concentration ($C_{ss,avg}$), and fluctuation index (FI).

DRV Substudy:

Based on the individual plasma concentration-time data, using the actual sampling times, pharmacokinetic parameters (as applicable) were derived from the bioanalytical results at Weeks 1, 2, and 4 for telaprevir (total and free concentrations) and Day -1 and Weeks 1 and 2 for DRV (total and free concentrations). Analysis of ritonavir PK was done based on plasma concentrations only; calculation of PK parameters was not performed. Unbound PK parameters were determined using only the time points at which protein binding was determined (Day -1 and Week 2). The obtained total concentrations at these time points were corrected for the corresponding fraction unbound. The unbound fractions of telaprevir obtained at Week 1 were also reported.

Statistical analysis of DRV PK parameters was performed by comparing Week 2 (test) to Day -1 (reference).

Safety:

Safety parameters were tabulated and analyzed descriptively.

The results of the HIV-1 viral genotypes were evaluated by the protocol virologist. The frequency of International Antiviral Society (IAS)-USA protease (PR) and reverse transcriptase (RT) mutations were presented descriptively. The detection of HIV-1 resistance-associated mutations were not regarded as AEs.

PK/PD:

Pharmacokinetic-pharmacodynamic relationships with regards to both safety and efficacy were evaluated.

RESULTS:

STUDY POPULATION:

The FA set consisted of 162 subjects, of whom 64 were HCV treatment-naïve and 98 were HCV treatment-experienced (ie, 29 prior relapsers and 69 prior nonresponders [18 prior partial responders and 51 prior null responders]).

The majority of subjects had completed the study (107 [66.0%] subjects) at the time of the cutoff for primary analysis; 27 (16.7%) subjects were still ongoing in the study and 28 (17.3%) subjects had discontinued the study prematurely. The main reasons for premature study discontinuation were withdrawal of consent (12 [7.4%] subjects) or lost to follow-up (8 [4.9%] subjects). Premature study discontinuations were more frequent in subjects who were relapsers to their prior HCV treatment than in HCV treatment-naïve subjects and prior nonresponders. This was due to a higher rate of withdrawal of consent in prior relapsers than in the other prior HCV treatment response categories.

Study Termination; FA Set

		Treatment-experienced			
	Treatment-naive (N=64)	All Treatment-experienced (N=98)	Prior Relapsers (N=29)	Prior Non-responders (N=69)	All Subjects (N=162)
Type/Reason, n(%)					
Completed	45 (70.3%)	62 (63.3%)	14 (48.3%)	48 (69.6%)	107 (66.0%)
Discontinued	11 (17.2%)	17 (17.3%)	8 (27.6%)	9 (13.0%)	28 (17.3%)
Adverse event	1 (1.6%)	0	0	0	1 (0.6%)
Lost to follow-up	5 (7.8%)	3 (3.1%)	1 (3.4%)	2 (2.9%)	8 (4.9%)
Subject ineligible to continue the trial	0	3 (3.1%)	1 (3.4%)	2 (2.9%)	3 (1.9%)
Withdrawal by subject	3 (4.7%)	9 (9.2%)	5 (17.2%)	4 (5.8%)	12 (7.4%)
Other	2 (3.1%)	2 (2.0%)	1 (3.4%)	1 (1.4%)	4 (2.5%)
Ongoing	8 (12.5%)	19 (19.4%)	7 (24.1%)	12 (17.4%)	27 (16.7%)

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

The majority of the subjects were male (78.4%) and Caucasian (92.0%). Slightly more than half of the subjects were between 45 and 65 years of age (53.1%); median (range) age was 46.0 (20; 67) years. Subjects' median (range) BMI was 24.00 (18.5; 36.5) kg/m².

The majority of the subjects (87.0%) had high baseline HCV RNA, defined as HCV RNA ≥800,000 IU/mL. Based on liver biopsy or fibroscan (before or at screening), the majority of the subjects had no or minimal fibrosis (51.9%) or portal fibrosis (17.9%); 17.3% of subjects had bridging fibrosis and 13.0% of subjects had cirrhosis.

According to the NS5B HCV genotyping screening test, 65.6% of the subjects had HCV genotype 1a and 33.8% of the subjects had HCV genotype 1b. One subject had genotype 1l according to the NS5B assay. According to IL28B genotyping, 27.5% of the subjects had the IL28B genotype CC. The CT and TT genotypes were observed in 54.4%, and 18.1% of the subjects, respectively.

All subjects who entered the study had HIV-1 RNA <50 copies/mL during the screening phase (ie, at the screening visit or at a subsequent confirmation visit), as per inclusion criteria. At baseline, all but 3 subjects (98.1%) had HIV-1 RNA <50 copies/mL. Median (range) $CD4^+$ cell count at baseline was 0.65 (0.3; 1.6) x10E9 cells/L. All subjects were on a stable HAART regimen at screening, as per selection criteria. In the majority of the subjects, that stable HAART regimen at screening contained EFV (40.1%) or ATV/r (36.4%). Seventeen (10.5%) subjects each were on a stable HAART regimen that included DRV or RAL, and 4 (2.5%) subjects were on an ETR-based HAART regimen.

EFFICACY RESULTS:

Primary Efficacy Parameter:

The $SVR12_{planned}$ rate (95% CI) was 64.1% (51.1%, 75.7%) in HCV treatment-naïve subjects, 62.1% (42.3%, 79.3%) in prior relapsers, and 49.3% (37.0%, 61.6%) in prior nonresponders. Prior nonresponders further subdivided into prior partial responders and prior null responders yielded $SVR12_{planned}$ rates (95% CI) of 72.2% (46.5%, 90.3%) and 41.2% (27.6%, 55.8%), respectively.

In all prior HCV treatment response categories, $SVR12_{planned}$ rates were higher than the historical control SVR rates.

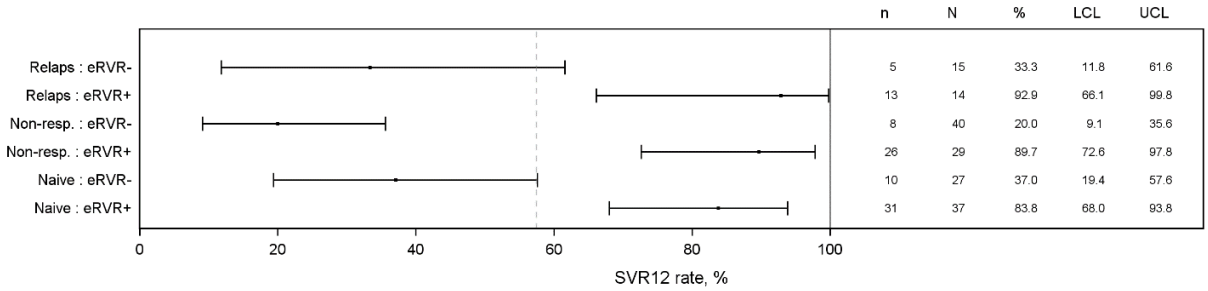
$SVR12_{planned}$ Rates (Snapshot)

	Treatment-naive	Treatment-experienced		
		All Treatment-experienced	Prior Relapsers	Prior Non-responders
Virologic response type				
$SVR12_{planned}$ (Snapshot)				
N	64	98	29	69
n (%)	41 (64.1%)	52 (53.1%)	18 (62.1%)	34 (49.3%)
95% CI	[51.1%;75.7%]	[42.7%;63.2%]	[42.3%;79.3%]	[37.0%;61.6%]
Historical control SVR	29%[a]		18%[b]	7%[b]

N: number of subjects with data, n: number of subjects with that observation
CI = Exact 95% (Clopper-Pearson) confidence interval
[a] Torriani et al., 2014; [b] SVR rates from the monoinfection studies (Study 108 and Study C216) with a scaling factor of 75%

In all prior HCV treatment response categories, $SVR12_{planned}$ rates were higher in subjects who achieved eRVR compared to subjects who did not achieve eRVR (see figure below). Overall, attainment of eRVR was a good predictor of SVR. Among subjects who achieved eRVR, 87.5% achieved SVR, compared to 28.0% in subjects who did not achieve eRVR.

$SVR12_{planned}$ (Snapshot) Rates by eRVR Status



Dashed reference line: SVR rate of the overall population: 57.41 %
n: number of subjects with SVR; N: number of subjects with data; LLC: lower limit of the 95% CI; ULC: upper limit of the 95% CI.
Source: TEFSVR20

eRVR+: achieved eRVR, eRVR-: did not achieve eRVR
N: number of subjects with data, n: number of subjects with $SVR12_{planned}$ (Snapshot)
CI = Exact 95% (Clopper-Pearson) confidence interval, LCL: lower confidence level, UCL: upper confidence level

In HCV treatment-naïve subjects who had eRVR and did not have cirrhosis (planned treatment duration of 24 weeks), the $SVR12_{planned}$ rate was 83.8% (95% CI [68.0%, 93.8%]), whereas in HCV treatment-naïve subjects who did not have eRVR or had cirrhosis (planned treatment duration of 48 weeks), the $SVR12_{planned}$ rate was 37.0% (95% CI [19.4%, 57.6%]). In prior relapsers who had eRVR and did not have cirrhosis (planned treatment duration of 24 weeks), the $SVR12_{planned}$ rate was 92.3% (95% CI [64.0%, 99.8%]), whereas in prior relapsers who did not have eRVR or had cirrhosis (planned treatment duration of 48 weeks), the $SVR12_{planned}$ rate was 37.5% (95% CI [15.2%, 64.6%]).

On-Treatment Virologic Response:

The RVR and eRVR rates in this study are summarized in the table below.

RVR and eRVR Rates

	Treatment-naive	Treatment-experienced		
		All Treatment-experienced	Prior Relapsers	Prior Non-responders
Virologic response type				
RVR (NC=F)				
N	64	98	29	69
n (%)	39 (60.9%)	46 (46.9%)	17 (58.6%)	29 (42.0%)
95% CI	[47.9%;72.9%]	[36.8%;57.3%]	[38.9%;76.5%]	[30.2%;54.5%]
eRVR (NC=F)				
N	64	98	29	69
n (%)	37 (57.8%)	43 (43.9%)	14 (48.3%)	29 (42.0%)
95% CI	[44.8%;70.1%]	[33.9%;54.3%]	[29.4%;67.5%]	[30.2%;54.5%]

N: number of subjects with data, n: number of subjects with that observation
CI = Exact 95% (Clopper-Pearson) confidence interval

Treatment Outcome:

An overview of the treatment outcome, including reasons for not achieving $SVR12_{planned}$ is summarized in the table below.

Treatment Outcome (Snapshot)

	Treatment-naive	Treatment-experienced		
		All Treatment-experienced	Prior Relapsers	Prior Non-responders
Treatment outcome type/Category/Subcategory, n(%)				
Treatment outcome (Snapshot)	64 (100.0%)	98 (100.0%)	29 (100.0%)	69 (100.0%)
$SVR12_{planned}$ (Snapshot)	**41 (64.1%)**	**52 (53.1%)**	**18 (62.1%)**	**34 (49.3%)**
Relapse (Snapshot)[a]	**4 (6.3%)**	**4 (4.1%)**	**1 (3.4%)**	**3 (4.3%)**
On treatment virologic failure	**14 (21.9%)**	**27 (27.6%)**	**1 (3.4%)**	**26 (37.7%)**
Week 4 Stopping Rule	2 (3.1%)	7 (7.1%)	0	7 (10.1%)
Week 8 Stopping Rule	1 (1.6%)	4 (4.1%)	0	4 (5.8%)
Week 12 Stopping Rule	2 (3.1%)	4 (4.1%)	0	4 (5.8%)
Week 24 Stopping Rule	5 (7.8%)	7 (7.1%)	0	7 (10.1%)
Week 36 Stopping Rule	2 (3.1%)	5 (5.1%)	1 (3.4%)	4 (5.8%)
Viral Breakthrough	2 (3.1%)	0	0	0
Other	**5 (7.8%)**	**15 (15.3%)**	**9 (31.0%)**	**6 (8.7%)**
HCV RNA ≥ 25 IU/mL at actual EOT	0	5 (5.1%)	2 (6.9%)	3 (4.3%)
HCV RNA < 25 IU/mL at actual EOT and at least once HCV RNA ≥ 25 IU/mL thereafter	1 (1.6%)	2 (2.0%)	0	2 (2.9%)
HCV RNA < 25 IU/mL at actual EOT and never HCV RNA ≥ 25 IU/mL thereafter	3 (4.7%)	7 (7.1%)	6 (20.7%)	1 (1.4%)
Other	1 (1.6%)	1 (1.0%)	1 (3.4%)	0

n: number of subjects with that observation; EOT: end of HCV treatment
[a] The denominator for relapse in this table is the total number of subjects with data.

The $SVR24_{planned}$ rates were 64.1%, 65.5%, and 49.3% in HCV treatment-naïve subjects, prior relapsers, and prior nonresponders, respectively. All subjects who achieved SVR12 also achieved SVR24. In addition, one prior relapser who missed the SVR12 assessment achieved SVR24. In the primary analysis (SVR12), this subject had been assigned to the treatment outcome category "HCV RNA <25 IU/mL at actual end of HCV treatment (EOT) and never HCV RNA ≥25 IU/mL thereafter".

VIROLOGY RESULTS:

The number of subjects with higher-level or lower-level telaprevir-resistant variants at time of failure was 17 of the 64 HCV treatment naïve subjects (26.6%), 28 of the 69 prior nonresponders (40.6%), and 2 of the 29 prior relapsers (6.9%). The highest frequency of telaprevir-resistant variants at time of failure was observed in prior nonresponder subjects. On-treatment virologic failure was associated with mainly higher-level telaprevir-resistant variants (with the highest proportion in genotype 1a). The majority of subjects who relapsed had lower-level telaprevir-resistant variants.

Although numbers are low and median follow-up time is limited in the final analysis, telaprevir-resistant variants became undetectable by population sequencing over time in the absence of telaprevir selective pressure. The rate of loss of telaprevir-resistant variants in genotype 1a appears to be lower than variants in genotype 1b.

PHARMACOKINETIC RESULTS:

Telaprevir Pharmacokinetics - Population Pharmacokinetics:

The 12-week Bayesian feedback population PK analysis was performed based on sparse blood sampling for telaprevir from the main study (1 sample per subject anytime postdose on Weeks 2, 4, and 8) and rich blood sampling from the PK substudy (predose and several time points postdose at least 2 weeks and up to 4 weeks after initiation of study drug). The individual pharmacokinetic parameters and exposure metrics for telaprevir at the Week 12 population PK analysis of this study were determined. Mean (SD) C_{0h} and C_{maxss} were 2510 (846) ng/mL and 3430 (1020) ng/mL, respectively. Mean (SD) AUC_{24} was 74200 (22700) ng.h/mL.

ARV Pharmacokinetics - Sparse Sampling for ARVs in the Main Study:

Plasma concentrations of ABC, ETR, RAL, raltegravir glucuronide (the circulating metabolite of RAL), and ritonavir remained generally constant during the weeks of sparse sampling for ARVs in the main study. No difference between baseline levels and levels during telaprevir treatment was observed. There was a large intersubject variability in DRV plasma concentrations and a trend towards higher DRV plasma concentrations in the absence of telaprevir, at baseline and Week 24, was observed.

DRV Substudy:

Full PK profiles of DRV (total and unbound) and ritonavir (total) were available for 17 subjects for DRV/r at 800/100 mg qd-based HAART regimen (Day -1) and for 16 subjects for DRV/r at 800/100 mg qd-based HAART regimen combined with telaprevir at 750 mg q8h, Peg-IFN-alfa-2a at 180 µg/week and RBV at 800 mg/day (Week 2). Full PK profiles of telaprevir (total and unbound) were available for 16 subjects at Week 2.

Telaprevir and DRV exposures (total and unbound) were reduced after administration of the DRV/r 800/100 mg qd-based HAART regimen with telaprevir 750 mg q8h, Peg IFN-alfa-2a, and RBV in HCV/HIV coinfected subjects. The mean total plasma concentrations for ritonavir were generally similar after intake at Week 2 as compared to Day -1.

SAFETY RESULTS:

Adverse Events:

A summary table of AEs, the most frequently reported AEs, and Special Search Category (SSC) AEs are presented in the table below.

Summary Table of Adverse Events; FA Set

	Telaprevir treatment phase (N=162)
Type, n(%)	
Any AE	157 (96.9%)
Death	0
Any SAE	9 (5.6%)
Any AE of at least grade 3	53 (32.7%)
Any AE of grade 4	19 (11.7%)
Any AE leading to permanent discontinuation of telaprevir	14 (8.6%)
Any AE leading to permanent discontinuation of Peg-IFN	12 (7.4%)
Any AE leading to permanent discontinuation of RBV	12 (7.4%)
Any AE at least possibly related to telaprevir[a]	134 (82.7%)
Any AE at least possibly related to Peg-IFN[a]	144 (88.9%)
Any AE at least possibly related to RBV[a]	122 (75.3%)
Most Frequently Reported AEs (>25.0% of the Subjects) During the Telaprevir Treatment Phase	
Pruritus	70 (43.2%)
Fatigue	44 (27.2%)
Rash	43 (26.5%)
Special Search Category Events[b]	
Anemia SSC	24 (14.8%)
SAE	4 (2.5%)
At least grade 3	5 (3.1%)
Pruritus SSC	70 (43.2%)
SAE	0
At least grade 3	5 (3.1%)
Rash SSC	55 (34.0%)
SAE	1 (0.6%)
At least grade 3	4 (2.5%)
Anorectal signs and symptoms SSC	48 (29.6%)
SAE	0
At least grade 3	3 (1.9%)
Injection site reaction SSC	12 (7.4%)
SAE	0
At least grade 3	0
ECG/QT SSC	0

[a] investigator causality assessment
[b] Special Search Categories were created by grouping AE terms that represent similar medical concepts, from the same or different body systems, to ensure that each subject with an event included within a predefined SSC was counted but counted only once.
N: number of subjects with data, n: number of subjects with that observation

None of the subjects died during the treatment phase. One subject died during the follow-up phase (intestinal ischemia, large intestine perforation, and infectious peritonitis, considered unlikely related to any of the HCV study drugs by the investigator).

By preferred term, the most frequently reported AEs (in >25.0% of the subjects) during the telaprevir treatment phase were pruritus (43.2%), fatigue (27.2%), and rash (26.5%).

Incidences of anemia, rash, pruritus, anorectal signs and symptoms, and injection site reaction SSC events that were serious, or at least grade 3 severity, or led to permanent discontinuation of telaprevir were low. None of the subjects experienced an event within the ECG/QT SSC, during the telaprevir treatment phase.

Clinical Laboratory Tests:

The most frequently observed graded laboratory abnormalities (in >35.0% of the subjects) emerging during the telaprevir treatment phase were platelets decreased (58.9%), hyperuricemia (58.4%), neutrophils decreased (41.3%), leukocytes decreased (38.1%), cholesterol increased (36.1%), and hyperbilirubinemia (35.4%). The most frequently observed laboratory abnormalities of at least grade 3 (in >5.0% of the subjects) emerging during the telaprevir treatment phase were hyperbilirubinemia (23.0%), platelets decreased (5.7%), and neutrophils decreased (5.6%).

Adverse events related to clinical laboratory tests emerging during the telaprevir treatment phase were most often anemia (13.6%), thrombocytopenia (11.1%), hyperbilirubinemia (6.2%), neutropenia (4.9%), and blood bilirubin increased (3.1%). All others were reported in at most 3 (1.9%) subjects.

HIV-1 Parameters:

Three subjects showed a HIV viral breakthrough with HIV-1 RNA ≥200 copies/mL at their last HIV-1 viral load assessment; this was after telaprevir treatment, during the follow-up phase for all 3 subjects. All 3 subjects had at least 1 IAS-USA HIV resistance mutation related to their HAART regimen at the time of breakthrough.

Median $CD4^+$ count decreased from baseline to Week 12, with the steepest change from baseline to Week 4 (first $CD4^+$ assessment; median [range] $CD4^+$ count at baseline: 0.6505 [0.277; 1.551] x10E9 cells/L; median [range] change from baseline at Week 4: -0.1948 [-0.780; 0.043] x10E9 cells/L) and remained relatively stable thereafter. Treatment-emergent $CD4^+$ count below normal range was reported in 50.6% of the subjects.

No AIDS-defining illnesses were reported during the study.

ECG and Vital Signs:

Mean changes in ECG and vital sign parameters were generally small. None of the observed changes were considered to be clinically relevant.

None of the subjects had a QTcF value >480 ms and no QTcF increases from baseline >60 ms were observed during the telaprevir treatment phase.

None of the vital sign abnormalities were grade 3.

Incidences of vital sign- and ECG-related AEs were low (at most 2.5% of the subjects during the telaprevir treatment phase).

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

Investigation of the relationship between drug exposure and $SVR12_{planned}$ indicated no relevant differences in the range of $AUC_{24,ss}$ and $C_{trough,ss}$ values between subjects who did and did not achieve $SVR12_{planned}$.

STUDY LIMITATIONS:

While the sample size was sufficient to meet the objectives of the study, the sample size was not large enough to allow reliable interpretations of some of the subgroup analyses. Many of the subgroups consisted of a low number of subjects and this resulted in wide 95% CIs. Therefore, conclusions on subgroup analyses should be undertaken cautiously.

CONCLUSION(S):

Results of this Phase 3 study in 162 subjects coinfected with HCV-1/HIV-1 who were on a stable HAART regimen for HIV demonstrated that the $SVR12_{planned}$ rates with telaprevir in combination with Peg-IFN-alfa-2a and RBV were higher than historical control SVR rates derived from literature in HCV-1/HIV-1-coinfected subjects treated with Peg-IFN and RBV.

Antiviral efficacy of response-guided therapy of 12 weeks telaprevir plus 24 or 48 weeks of Peg-IFN-alfa-2a and RBV in HCV treatment-naïve subjects and HCV treatment-experienced prior relapser subjects coinfected with HCV-1/HIV-1 was shown.

On-treatment virologic failure was associated with mainly higher-level telaprevir-resistant variants (with the highest proportion in genotype 1a). Relapse was mainly associated with lower-level telaprevir-resistant variants.

Mean (SD) C_{0h}, C_{maxss}, and AUC_{24} computed from Week 12 population PK analysis were 2510 (846) ng/mL, 3430 (1020) ng/mL, and 74200 (22700) ng.h/mL, respectively.

Plasma concentrations of ABC, ETR, RAL, raltegravir glucuronide (the circulating metabolite of RAL), and ritonavir were constant throughout coadministration of the HIV ARVs and telaprevir in combination with Peg-IFN and RBV, and similar to baseline. There was a large intersubject variability in DRV plasma concentrations and the sparse sampling data indicated a trend towards higher DRV plasma concentrations in the absence of telaprevir. In the DRV substudy, DRV plasma concentrations were reduced after administration of the DRV/r 800/100 mg qd-based HAART regimen and telaprevir 750 mg q8h, Peg-IFN-alfa-2a and RBV in HCV/HIV coinfected subjects.

Telaprevir in combination with Peg-IFN alfa-2a and RBV and permitted HIV ARVs was generally safe and well tolerated.

The majority of the subjects maintained HIV suppression during the study. Three subjects showed a HIV viral breakthrough with HIV-1 RNA $\geq$200 copies/mL, all of which were during follow-up at their last HIV-1 viral load assessment. All 3 subjects had at least 1 IAS-USA HIV resistance mutation related to their HAART regimen at the time of breakthrough.

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