SYNOPSIS

Name of Sponsor/Company	Janssen*
Name of Finished Product	INCIVO/INCIVEK
Name of Active Ingredient(s)	VX-950 (telaprevir)

* Janssen is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen R&D Ireland; or Janssen Research & Development, LLC. The term "sponsor" is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved

Date: 30 October 2014

Prepared by: Janssen-Cilag International NV

Protocol No.: VX-950HEP3002

Title of Study: Multicenter, Open-Label, Early Access Program of Telaprevir in Combination With Peginterferon Alfa and Ribavirin in Genotype 1 Chronic Hepatitis C Subjects With Severe Fibrosis and Compensated Cirrhosis

EudraCT Number: 2010-023669-23

NCT No.: NCT01508286

Clinical Registry No.: CR017857

Coordinating Investigator: Prof. Massimo Colombo, MD, 1st Division of Gastroenterology, Fondazione IRCCS Ca` Granda Ospedale Maggiore Policlinico, Universita` degli Studi di Milano, Milan, Italy

Study Center(s): 181 sites in 16 countries: Italy (47 sites), Spain (28 sites), Russia (16 sites), Belgium (11 sites), Germany (11 sites), Australia (10 sites), Romania (10 sites), Greece (9 sites), Hungary (8 sites), Austria (6 sites), Brazil (6 sites), Switzerland (6 sites), Czech Republic (5 sites), Serbia (4 sites), New Zealand (3 sites), and Luxembourg (1 site).

Publication (Reference):

Representative publications of data from the interim analyses:

- Colombo M, Fernández I, Abdurakhmanov D, et al. Safety and on-treatment efficacy of telaprevir: the early access programme for patients with advanced hepatitis C. Gut. 2014 Jul 63(7):1150-8.
- Palescandolo E, Vijgen L, Talloen W et al. Prediction of severe cutaneous reactions during triple therapy in HCV: validation of a G WAS candidate genetic marker. Journal of Hepatology. 2014;60(1):S490-S491.
- Colombo M, Strasser SI, Moreno C, et al. Sustained virological response with telaprevir in 1078 patients with advanced hepatitis C: The international telaprevir access program. Journal of Hepatology. 2014 Nov 61(5):976-983.

Study Period: 31 May 2011 to 30 May 2014 (first to last observation recorded as part of the database)

Phase of Development: Phase 3 Early Access Program

Objectives:

The objectives of this early access program were to provide telaprevir for subjects with genotype 1 chronic hepatitis C with severe fibrosis and compensated cirrhosis who reside in countries in which telaprevir was not commercially available at the time of protocol writing and who were not eligible for enrollment into an ongoing clinical study of telaprevir, and to collect additional safety and tolerability data on telaprevir treatment in combination with Peg-IFN-alfa and RBV.

Methodology:

This was a multicenter, multinational, open-label, noncomparative early access program. All enrolled subjects were to receive telaprevir 750 mg q8h during the first 12 weeks of the early access program in combination with Peg-IFN-alfa/RBV. At Week 12, telaprevir dosing was to end and subjects were to continue on Peg-IFN-alfa and RBV only for an additional 12 or 36 weeks. The total treatment duration was determined based on virologic response to treatment and/or type of subject.

For all subjects, stopping rules based on virologic response at Weeks 4 and 12 were to be applied to ensure that telaprevir or Peg-IFN-alfa/RBV treatments were stopped if a subject had viral breakthrough or failure. In prior null responders, consideration was to be given to conduct an additional HCV RNA test at Week 8; if the HCV RNA concentration was >1,000 IU/mL, telaprevir, Peg-IFN-alfa, and RBV were to be discontinued. For guidelines on treatment discontinuation after Week 12, the local prescribing information for Peg-IFN-alfa and RBV was to be consulted.

Additional plasma HCV RNA levels were to be measured at Week 24 in subjects with a total treatment duration of 24 weeks and at Weeks 24 and 48 in subjects with a total treatment duration of 48 weeks. All subjects were to have a follow-up visit, including measurement of plasma HCV RNA levels, 24 weeks after the last administered dose of any HCV drug (telaprevir, Peg-IFN-alfa, or RBV).

Assessment of safety and tolerability was based on reported adverse events (AEs), clinical laboratory tests, vital sign measurements, ECG monitoring, and physical examinations.

An optional 8.5-mL blood sample was collected from subjects who consented to participate in the pharmacogenomic (deoxyribonucleic acid [DNA]) component of the early access program.

Number of Subjects (planned and analyzed):

Approximately 3,000 subjects residing in countries in which telaprevir was not commercially available at the time of protocol writing and not being eligible for enrollment into an ongoing clinical study of telaprevir were estimated to be enrolled in this early access program. Enrollment of subjects was continued until telaprevir became available for reimbursement in the participating countries, or until September 2013, whichever occurred first, unless other guidelines were applicable per local regulations.

The early access program was not designed to evaluate a specific statistical hypothesis but to provide subjects with early access to telaprevir. Therefore, the number of enrolled subjects was not based on statistical but rather practical considerations involving the expected prevalence of HCV infection in the countries included in the program and the projected number of eligible subjects based on major eligibility criteria along with other available therapies.

Overall 1,772 subjects received at least one dose of telaprevir (intent-treat set; ITT). In total 199 subjects were excluded from the efficacy evaluable (EE) set; the EE set consisted of 1,573 subjects who each received at least 1 dose of telaprevir.

Diagnosis and Main Criteria for Inclusion:

Men or women between 18 and 70 years of age (inclusive) with genotype 1 chronic hepatitis C and severe fibrosis (Metavir score F3 or Ishak stage 3-4) or cirrhosis (Metavir score F4 or Ishak stage 5-6), and compensated liver disease (Child-Pugh Grade A), who resided in a country in which telaprevir was not commercially available at the time of protocol writing, and who were not eligible for enrollment into an ongoing clinical study of telaprevir.

Test Product, Dose and Mode of Administration, Batch No.: telaprevir 375 mg tablets (Batch Nos: AGL3B00, AKL4T00, AKL4U00, BEL4000, AKL4V02, BEL2N00, AKL4T01, BJL3G00, 9GL0V)

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

Duration of Treatment:

Telaprevir during the first 12 weeks in combination with Peg-IFN-alfa/RBV for a total duration of 24 or 48 weeks, plus a follow-up visit 24 weeks after the last administered dose of HCV drug.

The duration of Peg-IFN-alfa/RBV was based on the following:

- Subjects with severe fibrosis (Metavir score F3 or Ishak stage 3-4) who were treatment-naïve or prior treatment relapsers were to be treated with Peg-IFN-alfa/RBV for an additional 12 or 36 weeks after the 12-week telaprevir combination treatment (total treatment duration of 24 or 48 weeks, respectively), based on virologic response to treatment:
    - additional 12 weeks of Peg-IFN-alfa/RBV in subjects with HCV RNA '<lower limit of quantification (LLOQ), target not detected' at Weeks 4 and 12;
    - additional 36 weeks of Peg-IFN-alfa/RBV in subjects with detectable HCV RNA at either Week 4 or 12;
- Previously-treated subjects with prior partial or prior null response, or subjects who had viral breakthrough, with severe fibrosis (Metavir score F3 or Ishak stage 3-4) and all subjects with cirrhosis (Metavir score F4 or Ishak stage 5-6) were to be treated with an additional 36 weeks of Peg-IFN-alfa/RBV (total treatment duration of 48 weeks).

Criteria for Evaluation:

Antiviral Activity Evaluations

Although there were no formal efficacy evaluations in this early access program, plasma HCV RNA levels were determined by the local laboratory and results were used as the basis for treatment-guided therapy. Plasma HCV RNA levels were collected at screening, Week 4, Week 12, Week 24 and Week 48.

Pharmacogenomic Evaluations

For subjects who consented in a separate pharmacogenomic (DNA) informed consent, 1 optional 8.5-mL blood sample was collected, preferably at baseline, for potential analysis of genetic variations in the interleukin-28B (IL28B) gene (single nucleotide polymorphisms [SNP] rs12979860), the inosine triphosphatase (ITPA) gene, or in genes associated with severe cutaneous adverse reactions.

The results of the pharmacogenomic evaluations are beyond the scope of this Clinical Study Report (CSR). They are described elsewhere (Palescandolo et al, 2014).

Safety Evaluations

Adverse events

At each visit from signing of the informed consent form onwards, the subject was asked about any untoward medical occurrences. All AEs were graded by means of the Division of AIDS (DAIDS) criteria, except for rash which has protocol-specific definitions of severity grades.

The following AEs were recorded:

- All serious adverse events (SAEs) occurring between signing of informed consent until completion of the last early access program-related procedure.
- The non-serious AEs occurring between the first dose of telaprevir and 30 days after the last dose of telaprevir:
  - All rash and anemia events, regardless of (DAIDS) grade or relationship to telaprevir;
  - AEs considered at least possibly related to telaprevir by the investigator:
    - ✓ All AEs with DAIDS Grade 2 (moderate) or higher (including laboratory abnormalities);
    - ✓ Other AEs (ie, DAIDS Grade 1 [mild]) considered medically significant (eg, required medical intervention) (including laboratory abnormalities);
  - All AEs leading to discontinuation of telaprevir, regardless of DAIDS grade or relationship to telaprevir;
  - Any pregnancy in female subjects or in female partners of male subjects;
  - Special reporting situations: overdose, suspected abuse/misuse, inadvertent or accidental exposure, or medication error of telaprevir;
  - Other AEs as per local regulations only.

Clinical laboratory tests (hematology, serum chemistry):

Clinical laboratory tests were performed by local laboratories. Samples were obtained at screening, on Day 1 predose (baseline), and at Weeks 2, 4, 8, 12, 24, and 48, or at time of discontinuation.

Vital sign measurements

Pulse and blood pressure were to be measured at screening, on Day 1 predose (baseline), and at Weeks 2, 4, 8, 12, 24, and 48, or at time of discontinuation.

Physical examinations

A complete physical examination was to be performed at screening. At all other visits up to 30 days after the last dose of telaprevir, physical examinations were to be directed at detecting AEs. Only those signs and symptoms that represented clinically important changes, whether serious or nonserious, meeting the criteria for reporting of AEs were to be recorded on the eCRF. All physical examinations performed more than 30 days after the last dose of telaprevir were to be completed according to clinical practice.

Electrocardiogram

Electrocardiogram monitoring was recommended at the screening visit to assess clinically significant ECG abnormalities.

Statistical Methods:

This early access program was designed to provide subjects with early access to telaprevir and was not intended to evaluate a specific statistical hypothesis. All subjects in the program received open-label telaprevir in addition to Peg-IFN-alfa and RBV. As such, no inferential statistical analyses were planned.

Analyses were performed for descriptive purposes and were conducted using descriptive statistics along with 95% CIs.

The entire final analysis was performed on the intent-to-treat (ITT) set, defined as all enrolled subjects who received at least one dose of telaprevir. Subjects with any major protocol deviation that plausibly affected efficacy or subjects with HCV RNA '<LLOQ, target not detected' at EOT and without any HCV RNA follow-up assessment within the Week 24 Follow-up visit window (and who did not relapse before) were excluded from the efficacy evaluable (EE) set.

Antiviral Activity Endpoint

Endpoints related to antiviral activity were:

- Percentage of subjects achieving SVR 24 weeks after the last actual dose of HCV drug (telaprevir, Peg-IFN-alfa, or RBV) ($SVR24_{actual}$). Three definitions of $SVR24_{actual}$ were applied:
  - $SVR24_{actual}$ (Snapshot, <LLOQ), defined as achieving HCV RNA <LLOQ at the last nonmissing measurement in the Week 24 Follow-up visit window (ie, date from last intake of HCV drug [telaprevir, Peg-IFN-alfa, or RBV] +71 days until date of last contact);
  - $SVR24_{actual}$ (Snapshot, '<LLOQ, target not detected'), defined as achieving HCV RNA '<LLOQ, target not detected' at the last nonmissing measurement in the Week 24 Follow-up visit window;
  - $SVR24_{actual}$ (Classic), defined as having HCV RNA '<LLOQ, target not detected' at EOT, and having at least one nonmissing HCV RNA measurement in the Week 24 Follow-up visit window, and not having relapsed, and having completed treatment (all HCV drugs) or having permanently discontinued at least one of the HCV drugs but for a reason other than virologic failure.
- Change from baseline in $\log_{10}$ HCV RNA values at each time point during treatment;
- Percentage of subjects having virologic response (observed case) while on treatment;
- Percentage of subjects achieving rapid virologic response (RVR), defined as having virologic response at Week 4;
- Percentage of subjects achieving extended virologic response (eRVR), defined as having virologic response at Weeks 4 and 12;
- Percentage of subjects having virologic response at EOT (ie, Week 24 or 48, or earlier in case of early discontinuation of all HCV drugs [telaprevir, Peg-IFN-alfa, or RBV]);
- Percentage of subjects with viral breakthrough, defined as either
  - a confirmed increase >1 $\log_{10}$ in HCV RNA level from the lowest level reached during the considered treatment phase up to the considered time point, if the lowest level reached was >LLOQ, or
  - a confirmed value of HCV RNA >100 IU/mL in subjects whose HCV RNA had previously become <LLOQ (detectable or 'target not detected') during the considered treatment phase.
- Percentage of subjects who relapsed. Two definitions of viral relapse were applied:
  - Relapse (<LLOQ), defined as having HCV RNA <LLOQ at EOT and HCV RNA detectable during the follow-up phase, and not achieving $SVR24_{actual}$ (Snapshot, <LLOQ);
  - Relapse ('<LLOQ, target not detected'), defined similarly with the '<LLOQ, target not detected' threshold.
- Percentage of subjects who met a virologic stopping rule (see Table 1).

Safety Endpoints

Safety parameters were tabulated and analyzed descriptively.

RESULTS:

In total, 2,034 subjects were screened for this early access program; of these, 1,772 (87.1%) subjects were treated and 262 (12.9%) subjects were not. The main reasons for not being enrolled and treated were not fulfilling all inclusion and exclusion criteria (226 [11.1%] subjects) and withdrawal of consent (22 [1.1%] subjects).

Of the 1,772 subjects treated in this early access program, 20.0% were treatment-naïve for HCV (N=355). The remaining 80.0% had been treated earlier with Peg-IFN-alfa and RBV for HCV (N=1,417). Most of the HCV treatment-experienced subjects (55.1% of the treatment-experienced subjects) were prior nonresponders (N=781), whereas 41.4% were prior relapsers (N=586) and 3.5% had viral breakthrough during their earlier course of HCV treatment (N=49). The response category to prior HCV treatment was unknown for 1 subject. Of the 781 prior nonresponders, 63.4% were prior null responders (N=495), 30.0% were prior partial responders (N=234), and 6.7% were prior nonresponders for whom prior nonresponse was unspecified (N=52).

The majority of the subjects completed the early access program (1,587 [89.6%] subjects). The remaining 185 (10.4%) subjects had discontinued the program prematurely. Main reasons for premature discontinuation from the program were lost to follow-up (90 [5.1%] subjects) or withdrawal of consent (75 [4.2%] subjects). Eleven (11 [0.6%]) subjects discontinued the early access program due to AEs. Other reasons led to premature discontinuation from the program in less than 0.5% of the subjects.

Early Access Program Termination - ITT Set

	T12(q8h)/PR (N=1772)
Termination type, n (%)	
Completed	1587 (89.6%)
Discontinued	185 (10.4%)
Adverse event	11 (0.6%)
Lost To follow-up	90 (5.1%)
Subject entered another investigational trial	2 (0.1%)
Withdrawal by subject	75 (4.2%)
Other	7 (0.4%)
EE Set	1573 (88.8%)

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

The majority of the subjects were male (63.3%), White (98.3%) and between 45 and 65 years of age (72.0%) or older (7.7%). Mean (SD) age at screening was 53.0 (9.49) years. Subjects' mean (SD) Body Mass Index (BMI) at screening was 26.8 (3.99) kg/m².

The majority of the subjects (66.1%) had high baseline HCV RNA, defined as HCV RNA ≥800,000 IU/mL. Based on liver fibrosis test prior to screening, as per selection criteria, all subjects had cirrhosis (54.1%) or bridging fibrosis (45.5%), with the exception of 3 (0.2%) subjects who had no or minimal fibrosis and 3 (0.2%) subjects who had portal fibrosis.

According to HCV genotyping (lab test), 72.9% of the subjects had HCV genotype 1b and 21.4% had genotype 1a. The HCV genotype subtype was missing in 5.8% of the subjects. Of the 416 subjects who had IL28B genotyping results, 18.5% had the IL28B genotype CC, 61.5% had the CT genotype, and 20.0% had the TT genotype.

Response-guided treatment was applicable in treatment-naïve subjects and prior relapsers without cirrhosis: 29.9% of the HCV treatment-naïve subjects (106/355 subjects) and 25.8% of the prior relapsers

(151/586 subjects) had a planned HCV treatment duration of 24 weeks; the remaining subjects were planned to receive 48 weeks of HCV treatment.

EFFICACY RESULTS:

$SVR24_{actual}$ (Snapshot, <LLOQ) rates in this early access program were 73.8% in treatment-naïve subjects, 78.2% in prior relapsers, and 50.5% in prior nonresponders. Further subdivision of prior nonresponders into prior partial responders and prior null responders yielded $SVR24_{actual}$ rates of 60.3% and 44.0%, respectively.

Regardless of prior HCV treatment status, $SVR24_{actual}$ rates were higher in subjects with bridging fibrosis, genotype subtype 1b, IL28B genotype CC, and AFP ≤50 µg/L.

In subjects for whom response-guided treatment was applicable (treatment-naïve subjects and prior relapsers without cirrhosis), the $SVR24_{actual}$ rate was higher in subjects who had a planned treatment duration of 24 weeks compared to 48 weeks: 81.1% in the 106 treatment-naïve subjects who were planned to receive 24 weeks of HCV drugs compared to 71.3% in the 244 treatment-naïve subjects planned to have 48 weeks of treatment and 88.7% in the 151 prior relapsers who were planned to receive 24 weeks of HCV drugs compared to 75.9% in the 427 prior relapsers planned to have 48 weeks of treatment.

$SVR24_{actual}$ (Snapshot, '<LLOQ) Rates - ITT Set

	T12(q8h)/PR					
	Treatment naive (N=355)	Prior relapser (N=586)	Prior null responder (N=495)	Prior partial responder (N=234)	Prior non-responder + VB [a] (N=830)	Overall (N=1772)
$SVR24_{actual}$ (Snapshot, <LLOQ), n (%)						
No	93 (26.2%)	128 (21.8%)	277 (56.0%)	93 (39.7%)	411 (49.5%)	633 (35.7%)
Yes	262 (73.8%)	458 (78.2%)	218 (44.0%)	141 (60.3%)	419 (50.5%)	1139 (64.3%)

[a] This prior response category includes prior null responders, prior partial responders, subjects with unknown prior response, unspecified nonresponders, and viral breakthroughs (VB).
N: number of subjects with data, n: number of subjects with that observation

Rapid virologic response (RVR) rates were 63.9% in HCV treatment-naïve subjects, 69.6% in prior relapsers, and 50.7% in prior nonresponders. Extended rapid virologic response (eRVR) rates were 59.2% in HCV treatment-naïve subjects, 65.4% in prior relapsers, and 45.8% in prior nonresponders.

Attainment of eRVR was a good predictor of SVR: $SVR24_{actual}$ rates in all prior HCV treatment response categories were higher in subjects who achieved eRVR compared to subjects who did not achieve eRVR. Overall, among subjects who achieved eRVR, 78.1% achieved SVR, compared to 47.4% in subjects who did not achieve eRVR.

The RVR and eRVR rates were similar in subjects with bridging fibrosis compared to cirrhosis but higher in younger subjects, subjects with low baseline HCV RNA (<800,000 IU/mL), AFP ≤50 µg/L, and subjects with genotype subtype 1b.

The main reason for not achieving $SVR24_{actual}$ in HCV treatment-naïve subjects and prior nonresponders was viral breakthrough (7.9% and 19.3%) and relapse (7.9% and 14.7%). In prior relapsers, $SVR24_{actual}$ was most often not achieved because of relapse (7.5%).

Treatment Outcome by Prior Treatment Response - ITT Set

Treatment outcome type, n (%)	T12(q8h)/PR					
	Treatment naive (N=355)	Prior relapser (N=586)	Prior null responder (N=495)	Prior partial responder (N=234)	Prior non-responder + VB [a] (N=830)	Overall (N=1772)
1. $SVR24_{actual}$ (Snapshot, <LLOQ)	262 (73.8%)	458 (78.2%)	218 (44.0%)	141 (60.3%)	419 (50.5%)	1139 (64.3%)
2.1 VF: Relapse (<LLOQ)	28 (7.9%)	44 (7.5%)	69 (13.9%)	40 (17.1%)	122 (14.7%)	194 (10.9%)
2.2 VF: Viral breakthrough	28 (7.9%)	28 (4.8%)	122 (24.6%)	27 (11.5%)	160 (19.3%)	217 (12.2%)
2.3 VF: Met a stopping rule[b]	5 (1.4%)	8 (1.4%)	27 (5.5%)	7 (3.0%)	41 (4.9%)	54 (3.0%)
2.4 VF: >LLOQ at time point of SVR	1 (0.3%)	9 (1.5%)	18 (3.6%)	3 (1.3%)	22 (2.7%)	32 (1.8%)
2.5 VF: EOT >LLOQ and missing at time point of SVR	3 (0.8%)	1 (0.2%)	7 (1.4%)	0	9 (1.1%)	13 (0.7%)
2.6 VF: Other	0	1 (0.2%)	1 (0.2%)	2 (0.9%)	3 (0.4%)	4 (0.2%)
3.1 Other: Missing during treatment and Follow-up	4 (1.1%)	7 (1.2%)	3 (0.6%)	3 (1.3%)	8 (1.0%)	19 (1.1%)
3.2 Other: No Virologic Failure and missing Follow-up	24 (6.8%)	30 (5.1%)	30 (6.1%)	11 (4.7%)	46 (5.5%)	100 (5.6%)

[a] This prior response category includes prior null responders, prior partial responders, subjects with unknown prior response, unspecified nonresponders, and viral breakthroughs (VB).
[b] Note that the virologic stopping rules taken into account in this treatment outcome analysis are actual stopping rules (ie, derived from disposition and exposure data) and mathematical stopping rules (ie, derived from the HCV RNA data).
N: number of subjects with data; n: number of subjects with that observation; VF: virologic failure

In subjects with cirrhosis compared to subjects with bridging fibrosis, although higher incidences of reasons for not achieving $SVR24_{actual}$, in line with lower $SVR24_{actual}$ rates, the reasons for not achieving $SVR24_{actual}$ were similar.

SAFETY RESULTS:

Unless mentioned otherwise, only safety data during the telaprevir treatment phase are presented.

Adverse Events

Adverse events, including the most frequently reported AEs and Special Search Category (SSC) AEs, are presented in the table below.

Adverse Events During the Telaprevir Treatment Phase; FA Set

n (%)	T12(q8h)/PR Bridging fibrosis (F3) (N=813)	T12(q8h)/PR Cirrhosis (F4) (N=959)	T12(q8h)/PR Overall (N=1772)
Summary Table of Adverse Events			
Any AE	662 (81.4%)	804 (83.8%)	1466 (82.7%)
Any SAE	54 (6.6%)	93 (9.7%)	147 (8.3%)
Death	0	2 (0.2%)	2 (0.1%)
Any Grade 3 or 4 AE	274 (33.7%)	344 (35.9%)	618 (34.9%)
Any AE leading to permanent discontinuation of telaprevir	91 (11.2%)	130 (13.6%)	221 (12.5%)
Any AE leading to permanent discontinuation of RBV	48 (5.9%)	73 (7.6%)	121 (6.8%)
Any AE leading to permanent discontinuation of Peg-IFN-alfa	43 (5.3%)	68 (7.1%)	111 (6.3%)
Any AE considered at least possibly related to telaprevir by the investigator	640 (78.7%)	772 (80.5%)	1412 (79.7%)
Any AE considered at least possibly related to RBV by the investigator	564 (69.4%)	713 (74.3%)	1277 (72.1%)
Any AE considered at least possibly related to Peg-IFN-alfa by the investigator	356 (43.8%)	486 (50.7%)	842 (47.5%)
AEs by preferred term reported in >5.0% of the subjects			
Anaemia	415 (51.0%)	541 (56.4%)	956 (54.0%)
Rash	183 (22.5%)	250 (26.1%)	433 (24.4%)
Pruritus	110 (13.5%)	157 (16.4%)	267 (15.1%)
Asthenia	74 (9.1%)	80 (8.3%)	154 (8.7%)
Nausea	62 (7.6%)	85 (8.9%)	147 (8.3%)
Thrombocytopenia	38 (4.7%)	92 (9.6%)	130 (7.3%)
Anal Pruritus	36 (4.4%)	64 (6.7%)	100 (5.6%)
Special Search Category Events[a]			
Anemia SSC events	435 (53.5%)	562 (58.6%)	997 (56.3%)
Rash SSC events	230 (28.3%)	305 (31.8%)	535 (30.2%)
Pruritus SSC events	114 (14.0%)	163 (17.0%)	277 (15.6%)
Anorectal signs and symptoms SSC events	99 (12.2%)	140 (14.6%)	239 (13.5%)
Injection site reaction SSC events	1 (0.1%)	3 (0.3%)	4 (0.2%)
Thrombocytopenia SSC events	45 (5.6%)	103 (10.7%)	148 (8.4%)
Neutropenia SSC events	20 (2.5%)	32 (3.3%)	52 (2.9%)
ECG/QT SSC events	1 (0.1%)	2 (0.2%)	3 (0.2%)

Note: Bridging fibrosis (F3) also includes subjects with minimal fibrosis (F1) and portal fibrosis (F2).
N: number of subjects, n: number of subjects with that observation
[a] Special Search Categories (SSCs) were created by grouping AE terms that represent similar medical concepts, from the same or different SOCs, to ensure that each subject with an event included within a predefined SSC, is counted but counted only once.

In total 9 subjects died during the early access program; all but one had cirrhosis. For 2 of these subjects, the fatal AEs had their onset during the telaprevir treatment phase; one subject died from anemia, dehydration, hepatic failure, hepatorenal syndrome, hypercatabolism, hyperglycemia, ketoacidosis, multi-organ failure and renal failure, all considered possibly related to telaprevir by the investigator, and one subject died from bone marrow failure and multi-organ failure, considered unlikely and not related to telaprevir, respectively, by the investigator. Four subjects died from AEs with onset during treatment but after the telaprevir treatment phase (during treatment with Peg-IFN-alfa and RBV alone) and 3 subjects died from AEs that started during follow-up.

Serious AEs were reported in 8.3% of the subjects during the telaprevir treatment phase. Adverse events of at least grade 3 were reported in 34.9% of the subjects. Grade 4 AEs were reported in 3.8% of the subjects. In the majority of subjects, AEs were considered to be at least possibly related to telaprevir, Peg-IFN-alfa, and/or RBV by the investigator, in 79.7%, 47.5%, and 72.1% of the subjects, respectively.

Adverse events led to permanent discontinuation of telaprevir, Peg-IFN-alfa, or RBV in 12.5%, 6.3%, and 6.8% of subjects, respectively.

By preferred term, the most frequently reported AE (in >10.0% of the subjects) during the telaprevir treatment phase were anemia (54.0%), rash (24.4%), and pruritus (15.1%).

Approximately half of the subjects (56.3%) experienced an anemia SSC event during the telaprevir treatment phase. Rash and/or pruritus SSC events were reported in 38.5% of the subjects during the telaprevir treatment phase.

Clinical Laboratory Tests

Treatment-emergent abnormalities in hemoglobin, platelet and neutrophil count (any grade) during the telaprevir treatment period were observed in 94.2%, 68.4% and 48.5% of the subjects, respectively. Grade 3 and grade 4 w orst grade abnormalities were noted in 53.9% and 3.6% of the subjects, respectively, for hemoglobin, 9.2% and 0.8% of the subjects, respectively, for platelet count, and 7.0% and 1.4% of the subjects, respectively, for neutrophil count.

Vital Signs

Mean changes in vital sign parameters over time were generally small. Incidences of vital sign abnormalities and vital sign-related AEs were low.

STUDY LIMITATIONS:

No notable study limitations were identified. This is an early access program not designed to evaluate a specific statistical hypothesis but to provide subjects with early access to telaprevir.

CONCLUSION(S):

The results of this early access program confirm that treatment-naïve and experienced patients with bridging fibrosis or cirrhosis due to HCV genotype 1 who also have compensated liver disease can effectively and safely be treated with telaprevir triple therapy.

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