SYNOPSIS

Name of Sponsor/Company	Janssen EMEA*
Name of Finished Product	INCIVO®
Name of Investigational Product(s)	Telaprevir

* Janssen EMEA is an organization in Europe, the Middle East and Africa that operates through different legal entities in various countries. The legal entity acting as the sponsor for studies of Janssen EMEA may vary, such as, but not limited to Janssen Pharmaceutica NV or Janssen-Cilag International NV. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol as a separate document.

Status: Approved

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Prepared by: Janssen Pharmaceutica NV.

Protocol No.: VX-950HPC4017

Title of Study: Observational Multicenter Study in Ex-people who Inject Drugs (ex-PWIDs) to Evaluate Efficacy, Safety, and Adherence to Telaprevir in Combination With Pegylated Interferon Alfa and Ribavirin in Genotype 1 Chronic Hepatitis C Patients

NCT No.: NCT01980290

Clinical Registry No.: CR100966

Principal Investigator(s): This study was conducted at 18 sites each under the medical oversight of a principal investigator. No coordinating or overall principal investigator was assigned for this study.

Study Center(s): Belgium (6 sites), France (3 sites), Germany (4 sites), Netherlands (1 site), Switzerland (1 site), United Kingdom (3 sites).

Publication (Reference): None

Study Period: 06 May 2013 to 09 February 2015

Phase of Development: Non-interventional study.

Objectives: The primary objective was to evaluate the effectiveness, based on sustained virologic response (SVR) as measured by hepatitis C virus ribonucleic acid (HCV RNA) <25 IU/mL, at 12 weeks (SVR12) after the last dose of anti-HCV treatment (telaprevir, pegylated interferon alfa [Peg-IFN-alfa], ribavirin [RBV]), in ex-PWIDs with genotype 1 chronic hepatitis C under substitution therapy and/or followed in addiction centers and/or addiction programs.

[a] The term efficacy, as used in the protocol, relates to a controlled study (eg, a clinical trial). The term effectiveness, which refers to the outcome of the intent-to-treat (ITT) analysis, is more appropriate for a clinical practice setting and is used throughout this document. This change in terminology does not affect the planned objectives, measures or analyses.

Secondary Objectives

The secondary objectives were to assess:

- Adherence to telaprevir until Week 12 as measured by pill count and/or patient questionnaire (modified medication adherence self-report inventory [M-MASRI])

- Adherence to Peg-IFN-alfa and RBV (PR) treatment until end of treatment as measured by pill/vial count and/or patient questionnaire (M-MASRI)
- On-treatment virologic response (rapid virologic response [RVR], extended rapid virologic response [eRVR], Week 12, end of treatment) based on viral load, as measured by HCV RNA <25 IU/mL target not detected (TND)
- On-treatment virologic response (RVR*[a], eRVR*[b], Week 12, end of treatment) based on viral load, as measured by HCV RNA <25 IU/mL
- Tolerability and safety of telaprevir, in combination with PR
- Health-related quality of life based on patient-reported outcomes (PROs)
- Baseline and on-treatment predicting factors of SVR
- The virologic response (VR) rates in this study compared with historical data in ex- PWIDs treated with PR

[a] RVR* defined as a single Week 4 HCV RNA level <25 IU/mL

[b] eRVR*, defined as both the Week 4 and Week 12 HCV RNA levels <25 IU/mL

Methodology: This was a multicenter, prospective, observational study to evaluate the effectiveness, safety, tolerability, and adherence to telaprevir in ex-PWIDs. For each patient the data collected in this study was recorded at 6 time points (5 time points for patients who were administered PR treatment for 12 weeks) corresponding to routine care visits: baseline, and at the patient's routine care visit closest to Weeks 4, 12, and 24, end-of-treatment, and end-of-follow-up (approximately 12 weeks after end-of-treatment). No additional investigations or biological sampling were performed beyond the routine clinical management of the patient. Participating physicians offered enrollment to all eligible patients who they had planned to initiate on triple therapy with telaprevir, Peg-IFN-alfa, and RBV. The participation of a patient in this study did not impact on their standard of care or any benefits to which they were otherwise entitled. All aspects of treatment decisions and clinical management of patients were as per routine clinical practice, at the discretion of the treating physician.

Number of Patients (planned and analyzed): 115 patients planned; 46 patients analyzed; 26 patients completed.

Diagnosis and Main Criteria for Inclusion: Participating patients were men or women aged at least 18 years, who were infected with genotype 1 chronic hepatitis C, who had any fibrosis stage including compensated cirrhosis with a history of injecting drugs, and who had received substitution therapy (eg, methadone, buprenorphine) and/or were being followed in an addiction center and/or an addiction program. Participating patients were either treatment naïve or relapsed after IFN or Peg-IFN plus RBV.

Therapy, Dose and Mode of Administration, Batch No.: Telaprevir (375-mg tablets), Peg-IFN-alfa, and RBV were commercially sourced and were not provided or reimbursed by the sponsor. The dose and mode of administration was as in accordance with the approved local labeling.

Duration of Treatment: The duration of each patient's participation in this study was approximately 60 weeks.

Criteria for Evaluation:

Effectiveness: The primary endpoint was the percent of patients with SVR12, defined as HCV RNA level <25 IU/mL at 12 weeks after the last dose of anti-HCV treatment (telaprevir, Peg-IFN-alfa, and RBV). The secondary endpoints included percent of patients adherent to telaprevir, Peg-IFN-alfa and RBV; percent of patients with RVR (defined as a single Week 4 HCV RNA level <25 IU/mL TND) and RVR*(defined as a single Week 4 HCV RNA level <25 IU/mL); percent of patients with eRVR (defined

as both the Week 4 and Week 12 HCV RNA levels <25 IU/mL TND) and eRVR* (defined as both the Week 4 and Week 12 HCV RNA levels <25 IU/mL); and percent of patients with a HCV RNA level <25 IU/mL TND and <25 IU/mL at Week 12, Week 24, End-of-Treatment (telaprevir, Peg-IFN-alfa, and RBV), and End-of-Follow up.

PROs: Where permitted per local regulations, participating physicians were asked to obtain (or collect where available) PRO data from patients within the study, which included the EuroQoL-5 dimension (EQ-5D™) questionnaire, hospital anxiety and depression scale (HADS), alcohol use disorders identification test (AUDIT), and adherence to treatment (M-MASRI). Adherence to treatment was also to be recorded using pill/vial counts but those data were not analyzed since most patients did not provide their used medication packages for pill count.

Safety: Adverse events and special situations for telaprevir, together with clinical laboratory data, vital signs, and electrocardiogram (ECG) parameters, were documented in accordance with routine clinical practice. Adverse events of special interest included anemia and rash.

Statistical Methods:

Patient Information: The demographic and baseline disease characteristics were summarized descriptively.

Effectiveness: The primary endpoint was analyzed by tabulating the percentage of patients reaching SVR12 along with the 95% confidence interval (CI). There was no direct comparison for the primary analysis. Two definitions of SVR12 were applied: SVR12 (Snapshot, <25 IU/mL) and SVR12 (Snapshot, <25 IU/mL, TND). The secondary analyses were performed by tabulating the percent of patients (with 95% CI) reaching RVR, RVR*, eRVR, eRVR* as well as the percentage of patients with an HCV RNA level <25 IU/mL, TND and <25 IU/mL at Week 4, Week 12, Week 24, end-of-treatment (telaprevir, Peg-IFN-alfa, RBV), and end-of-follow-up. Summary statistics of prognostic factors for response were to be gathered from the historical control studies such that these factors could be used for adjustment and/or stratification factors in the historical control analysis.

Additional analyses were performed to evaluate the change from baseline in $\log_{10}$ HCV RNA values at each time point during treatment, the proportion of patients having VR (observed case) while on treatment, the proportion of patients with viral breakthrough, and the proportion of patients who relapsed.

PROs: The percentage and counts of patients' responses for each dimension were summarized for EQ-5D™. Patients' responses for HADS were summarized descriptively and categorically (normal, mild, moderate, and severe). In addition, patients who had depression (subtotal ≥8), anxiety (subtotal ≥8), or both were summarized with percentage and counts. AUDIT total score was summarized descriptively and categorically as <8 or ≥8. The percentage of patients adhering to telaprevir, Peg-IFN-alfa, and RBV were presented separately. The tabulation for M-MASRI included percentage and counts of the categorical adherence (0%, ≤10%, 10 ≤20%, up to 100%).

Safety: Adverse events, laboratory tests, vital signs, and ECG data collected during the study were summarized. Data were analyzed per study phase.

RESULTS:

STUDY POPULATION: In total 52 patients were screened, of whom 49 (94.2%) were treated and 3 (5.8%) were not treated due to not fulfilling all selection criteria.

Of the 49 patients who were treated, 46 had post-baseline assessments and were included in the ITT population. Of the 46 patients in the ITT population, 43 (93.5%) were treatment-naive and 3 (6.5%) were relapsers. Of the 34 patients in the evaluable for effectiveness (EE) population, 33 (97.1%) were treatment-naive and 1 (2.9%) was a relapser.

More than half of the patients in the ITT population completed the study (26 [56.5%] patients). The remaining 20 (43.5%) patients discontinued the program prematurely, mainly due to being lost to follow up (8 [17.4%] patients) or due to an adverse event (AE) (6 [13.0%] patients).

EFFECTIVENESS RESULTS: For the ITT population, the overall $SVR12_{actual}$ (Snapshot, <25 IU/mL) rate in this study was 54.3%. $SVR12_{actual}$ rates were 55.8% in HCV treatment-naïve and 33.3% for treatment-relapser patients.

For the EE population, the $SVR12_{actual}$ (Snapshot, <25 IU/mL) rate was 73.5%. $SVR12_{actual}$ rates were 72.7% in HCV treatment-naïve and 100.0% for the only treatment-relapser patient.

The overall RVR rate for the ITT population was 82.6%. Per prior HCV treatment response, RVR rates were 81.4% in HCV treatment-naïve and 100.0% in treatment-relapser patients. The eRVR rate in the study was 71.7%, or by prior HCV treatment response, 72.1% in HCV treatment-naïve and 66.7% in treatment-relapser patients. The RVR and eRVR rates were slightly higher in patients with nonexistent to minimal fibrosis than patients with bridging fibrosis or cirrhosis.

The overall RVR rate for the EE population was 85.3%. Per prior HCV treatment response, RVR rates were 84.8% in HCV treatment-naïve and 100.0% for the only treatment-relapser patient. The eRVR rate in the study was 79.4%, or by prior HCV treatment response, 78.8% in HCV treatment-naïve and 100.0% for the only treatment-relapser patient.

The main reason for patients in the ITT population not achieving $SVR12_{actual}$ was "other" (41.3%). Patients in this category had missing data at the follow up Week 12 window or had HCV RNA >25 IU/mL at SVR time point but neither had a relapse nor viral breakthrough. The reasons for missing data at follow up Week 12 were: protocol violation (1 patient), lost to follow up (8 patients), withdrawal by patient (2 patients), AE (2 patients) and other (4 patients).

The main reason for patients in the EE population not achieving $SVR12_{actual}$ was "other" (20.6%). Patients in this category had missing data at the follow up Week 12 window or had HCV RNA >25 IU/mL at SVR time point but neither had a relapse nor viral breakthrough.

Patient-Reported Outcomes Results

The findings from PRO questionnaires (EQ-5D™, HADS, and AUDIT) indicated that HCV treatment did not have any impact on the 5 dimensions of health outcome (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), levels of anxiety and depression, or alcohol intake.

SAFETY RESULTS:

Adverse Events

Evaluation of safety data is based on the ITT population set. No deaths were reported during the study. Nonfatal serious adverse events (SAEs) were reported in 24% of the patients during the HCV treatment phase. The majority of the patients (91%) had one or more AEs that emerged during the HCV treatment phase.

Telaprevir-related AEs during the HCV treatment phase were of at least grade 2 severity in 57% of the patients. Adverse events led to permanent discontinuation of telaprevir in 11% of the patients. Adverse events were considered to be at least possibly related to telaprevir in 70% of the patients with AEs during the HCV treatment phase.

By preferred term, the most frequently reported AEs (in ≥15.0% of patients) in the ITT population were anemia (39%), thrombocytopenia (30%), leukopenia (30%), fatigue (26%), pruritus (22%), nausea (17%), vomiting (15%), and headache (15%).

Special Search Categories

Anemia special search categories (SSC) events were reported in 41% of the patients during the HCV treatment phase in the ITT population. The majority of these anemia SSC events were of grade 1 or 2 severity; more severe anemia SSC events were reported in 11% of the patients. The patients with anemia SSC events who had at least one anemia SSC event that was considered to be at least possibly related to telaprevir by the investigator were reported in 12 (26% [at least Grade 2]) and 4 (9% [at least Grade 3]) patients. None of the anemia SSC events led to permanent discontinuation of telaprevir.

Rash and/or pruritus SSC events were reported in 39% patients during the HCV treatment phase in the ITT population. These rash and pruritus SSC events were of grade 1 or 2 severity in all patients except in 1 (2%) patient with grade 3 pruritus. The patients with rash or pruritus SSC events that were considered to be at least possibly related to telaprevir by the investigator were reported in 6 (13% [at least Grade 2]) and 1 (2% [at least Grade 3] patients. Only 1 (2%) patient had a rash SSC event that was serious. Incidences of rash SSC or pruritus SSC events that led to permanent discontinuation of telaprevir were low.

Clinical Laboratory Tests

Treatment-emergent abnormalities in hemoglobin, platelet and neutrophil count during the telaprevir treatment phase were observed in 81.4%, 72.1%, and 21.9% of the patients in the ITT population, respectively. Grade 3 and grade 4 (worst grade) abnormalities were noted in 25.6% and 11.6% of the patients, respectively, for hemoglobin, 9.3% and 4.7% of the patients, respectively, for platelet count, and 12.5% and 0% of the patients, respectively, for neutrophil count.

Vital Signs

There were no vital signs-related AEs or abnormalities in vital signs.

ECG

There were no ECG-related AEs or abnormalities in ECG parameters.

STUDY LIMITATIONS: A concurrent control arm was not included in this study since it was considered unethical. As such, despite attempts to control for external sources of variation, the secondary historical control comparison of telaprevir administered in combination with Peg-IFN-alfa and RBV versus combination treatment with Peg-IFN-alfa and RBV are to be interpreted with caution. While they provide some reference, lack of randomization could have balanced important prognostic factors across this study and the control.

CONCLUSION(S): In the 46 patients in the ITT population, who were ex-PWIDs with genotype 1 chronic hepatitis C under substitution therapy and/or followed in addiction centers and/or addiction programs, SVR12actual after the last dose of anti-HCV treatment (telaprevir, Peg-IFN-alfa, RBV) was 54.3%; SVR12actual rates were 55.8% for HCV treatment-naïve patients and 33.3% for treatment-relapser patients. For the 34 patients in the EE population, SVR12actual after the last dose of anti-HCV treatment (telaprevir, Peg-IFN-alfa, RBV) was 73.5%; SVR12actual rates were 72.7% for HCV treatment-naïve patients and 100.0% for the one treatment-relapser patient in this population.

The mean of the telaprevir treatment compliance until Week 12 and PR treatment compliance until End of Treatment was at or above 90% for all time points as measured by the patient questionnaire M-MASRI.

Telaprevir in combination with Peg-IFN-alfa and RBV was generally safe and well tolerated.