SYNOPSIS

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

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Status: Approved

Date: 3 May 2013

Prepared by: Janssen Infectious Diseases - Diagnostics BVBA

Protocol No.: VX-950HPC1001

Title of Study: A Phase I study to assess the safety and pharmacokinetics of telaprevir (VX-950) in subjects with moderate and severe hepatic impairment.

Study Name: VX-950HPC1001

EudraCT Number: 2012-001627-13

NCT No.: NCT01600976

Clinical Registry No.: CR100872

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Study Center(s): 2 centers, in Germany and Czech Republic

Publication (Reference): none at the time of this report

Study Period: 18 June 2012 to 6 November 2012

Phase of Development: I

Objectives:

The primary objective was to assess the pharmacokinetic parameters of telaprevir following administration of single and multiple oral doses of telaprevir in subjects with moderate hepatic impairment (Child-Pugh Score of 7-9; CPB), as compared to matched healthy subjects.

Secondary objectives were:

- to assess the safety of telaprevir following administration of single and multiple oral doses of telaprevir in subjects with CPB.
- to measure the unbound fractions of telaprevir after single and multiple doses of telaprevir in subjects with moderate hepatic impairment, as compared to matched healthy subjects.
- to assess any relationship between the measures of hepatic function (i.e., Child-Pugh score, albumin, bilirubin, alpha-1 acid glycoprotein [AAG], prothrombin time [PT]) and selected pharmacokinetic parameters of telaprevir in subjects with CPB and matched healthy subjects.

Exploratory objectives were:

- to assess the safety, tolerability, and pharmacokinetic parameters of telaprevir following administration of single and multiple oral doses of telaprevir in subjects with Child-Pugh score 10-12 (CPC).
- to measure the unbound fractions of telaprevir after single and multiple doses of telaprevir in subjects with severe hepatic impairment.

Methodology:

This was a Phase 1, open-label study of telaprevir. The study population was planned to consist of up to 24 subjects between 18 and 65 years old in 3 groups, i.e., 10 subjects with moderate hepatic impairment (Child-Pugh score 7-9; CPB) in Group 1, 10 healthy control subjects with normal hepatic function in Group 2, and up to 4 subjects with severe hepatic impairment (limited to Child-Pugh score 10-12; CPC) in Group 3. Each healthy control subject (Group 2) was matched to a subject with moderate hepatic impairment (Group 1) based on sex, age (± 5 years), and body mass index (BMI) (± 15%).

Initiation of enrolment and treatment of Groups 1, 2, and 3 occurred in a parallel manner. All subjects were to take telaprevir 750 mg every 8 hours (q8h) for 5 days followed by a single intake (morning dose) of telaprevir 750 mg on Day 6.

Blood samples for determination of plasma concentrations of telaprevir were taken at several time points. Rich pharmacokinetic profiles of telaprevir were measured on Day 1 (after a single dose of telaprevir) and Day 6 (at steady-state). For all subjects, additional blood samples were collected on Days 1 and 6 to estimate the unbound fractions of telaprevir. Sampling for protein binding was performed at predose and at 1, 4 and 8 hours after the (morning) intake of telaprevir on Days 1 and 6.

Safety and tolerability evaluations were recorded throughout the study period.

Number of Subjects (planned and analyzed):

The study population consisted of 24 subjects as planned, i.e., 10 subjects with moderate hepatic impairment, 10 healthy control subjects with normal hepatic function who were matched with regard to sex, age and BMI to the subjects with moderate hepatic impairment, and 4 subjects with severe hepatic impairment.

Diagnosis and Main Criteria for Inclusion:

Men or women between 18 and 65 years of age (extremes included), with BMI between 18.0 and 35.0 kg/m^2 (extremes included) could be included in the study.

Subjects were scored and classified into hepatic function groups according to the Child-Pugh classification, based upon physical examination and laboratory assessments at screening:

- Subjects with moderate hepatic impairment (Group 1) had to have a Child-Pugh score of 7 to 9 during screening and a history of hepatic disease that was to be documented in the Case Report form (CRF), such as hepatitis B, previous hepatitis C, alcoholic liver disease, autoimmune hepatitis, nonalcoholic fatty liver disease, hereditary/metabolic, cryptogenic, or other. Consistent with the disease process of hepatic impairment and associated symptoms, otherwise, subjects were to be in good health on the basis of a medical evaluation at screening.

- Healthy control subjects (Group 2) were to be matched to a subject with moderate hepatic impairment in Group 1 with regards to sex, age (± 5 years), and BMI (± 15%) and were to be healthy on the basis of a medical evaluation at screening.

- Subjects with severe hepatic impairment (Group 3) had to have a Child-Pugh score of 10 to 12 assessed during screening and hepatic impairment due to different etiologies such as hepatitis B, previous hepatitis C, alcoholic liver disease, autoimmune hepatitis, non-alcoholic fatty liver disease, hereditary/metabolic, cryptogenic, other. Consistent with the disease process of hepatic impairment and

associated symptoms, otherwise, subjects were to be in good health on the basis of a medical evaluation at screening.

Subjects with known allergies, hypersensitivity, or intolerance to telaprevir (VX-950) or its excipients could not be included in the study.

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

Telaprevir, administered as 375 mg tablet (F007) for oral administration under fed conditions (batch number BEL4001).

Duration of Treatment:

The study included a screening period of maximum 21 days, a treatment period of 6 days (5 days of telaprevir q8h administration followed by a single dose on Day 6), and a follow-up visit 5 to 7 days after last intake of study drug or early discontinuation.

Criteria for Evaluation:

PHARMACOKINETIC EVALUATIONS:

Venous blood samples in all 3 subject groups were collected for determination of blood plasma telaprevir concentrations on Days 1 and 6 (predose and 0.5, 1, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 9, 12, 15, and 18 hours after the morning dose of telaprevir; rich pharmacokinetic profiling), on Days 2 to 5 (predose), and in case of dropout. Additional samples for measurement of the fraction of unbound telaprevir were taken on Days 1 and 6 (predose and 1, 4, and 8 hours after the morning dose of telaprevir).

Based on the individual plasma concentration-time data, the following pharmacokinetic parameters were derived:

Total telaprevir:

- Day 1: parameters t_{max}, C_{max}, and AUC_{8h} for Groups 1, 2, and 3, and ratios $C_{max,\ Group\ 1/Group\ 2}$, $AUC_{8h,\ Group\ 1/Group\ 2}$, $C_{max,\ Group\ 3/Group\ 2}$, and $AUC_{8h,\ Group\ 3/Group\ 2}$
- Days 2 to 5: C_{0h} for Groups 1, 2, and 3
- Day 6: parameters C_{0h}, C_{min}, t_{max}, C_{max}, AUC_{8h}, CL/F, C_{avg}, and FI for Groups 1, 2, and 3, and ratios $C_{max,\ Day\ 6/Day\ 1}$, $AUC_{8h,\ Day\ 6/Day\ 1}$ (accumulation ratio), $C_{min,\ Group\ 1/Group\ 2}$, $C_{max,\ Group\ 1/Group\ 2}$, $AUC_{8h,\ Group\ 1/Group\ 2}$, $C_{min,\ Group\ 3/Group\ 2}$, $C_{max,\ Group\ 3/Group\ 2}$, and ratio $AUC_{8h,\ Group\ 3/Group\ 2}$

Unbound telaprevir:

- Day 1: parameters C_{max} and AUC_{8h} for Groups 1, 2, and 3, and ratios $C_{max,\ Group\ 1/Group\ 2}$, $AUC_{8h,\ Group\ 1/Group\ 2}$, $C_{max,\ Group\ 3/Group\ 2}$, and $AUC_{8h,\ Group\ 3/Group\ 2}$
- Day 6: parameters C_{0h}, C_{min}, C_{max}, AUC_{8h}, and CL/F for Groups 1, 2, and 3, and ratios $C_{max,\ Day\ 6/Day\ 1}$, $AUC_{8h,\ Day\ 6/Day\ 1}$ (accumulation ratio), $C_{min,\ Group\ 1/Group\ 2}$, $C_{max,\ Group\ 1/Group\ 2}$, $AUC_{8h,\ Group\ 1/Group\ 2}$, $C_{min,\ Group\ 3/Group\ 2}$, $C_{max,\ Group\ 3/Group\ 2}$, and $AUC_{8h,\ Group\ 3/Group\ 2}$

SAFETY EVALUATIONS:

Safety and tolerability were evaluated throughout the study from signing of the informed consent form (ICF) onwards until the last study-related visit. Adverse events (AEs) were reported for the duration of the study. Laboratory evaluations, electrocardiogram (ECG) and vital sign assessments, and physical examination were performed throughout the study.

Statistical Methods:

Descriptive statistics and frequency tabulations; a mixed-effect analysis of variance model including hepatic function as fixed effect was used to estimate the geometric least squares (GLS) means, intersubject variance, and corresponding 90% confidence intervals (CIs) of the ratios for pharmacokinetic parameters C_{max} and AUC for the difference in means on a log scale for the group of subjects with moderate hepatic impairment (Group 1) compared with the group of subjects with normal hepatic function (Group 2).

RESULTS:

STUDY POPULATION:

In total 24 subjects were enrolled and received at least one dose of study drug, i.e., 10 moderate hepatic impaired subjects (Group 1), 10 healthy control subjects matched to the subjects in Group 1 (Group 2), and 4 severe hepatic impaired subjects (Group 3). All subjects were exposed to the study drug as planned per protocol, except for one moderate hepatic impaired subject who interrupted study drug intake (3 doses on Day 3) due to an AE (head injury). All subjects completed the study.

All enrolled subjects were White and all but 4 subjects (i.e., 2 [20.0%] moderate hepatic impaired and 2 [20.0%] healthy control subjects) were male.

Median (range) age of the enrolled moderate hepatic impaired subjects and their matched healthy control subjects was 58.5 (48-65) and 59.5 (50-65) years, respectively. Their median (range) BMI was 26.70 (18.0-34.3) and 26.25 (20.7-31.1) kg/m^2, respectively.

Median (range) age of the 4 severe hepatic impaired subjects was 56.0 (54-59) years. Their median (range) BMI was 33.45 (29.5-34.9) kg/m^2.

PHARMACOKINETIC RESULTS:

Total telaprevir

A summary of key pharmacokinetic parameters of total telaprevir for all 3 groups and the statistical results comparing the pharmacokinetic parameters of total telaprevir between subjects with moderate hepatic impairment and healthy control subjects are provided in the table below:

Pharmacokinetics of total telaprevir (mean ± SD, t_{max}: median [range])	**750 mg q8h telaprevir on Days 1 to 5 + morning dose of 750 mg telaprevir on Day 6 in healthy control subjects (reference)**	**750 mg q8h telaprevir on Days 1 to 5 + morning dose of 750 mg telaprevir on Day 6 in subjects with moderate hepatic impairment (test)**	**750 mg q8h telaprevir on Days 1 to 5 + morning dose of 750 mg telaprevir on Day 6 in subjects with severe hepatic impairment**
N	10	10	4
Day 1			
C_{max}, ng/mL	2889 ± 1244	2030 ± 829	1920 ± 571
t_{max}, h	3.50 (3.00 - 6.00)	4.00 (2.50 - 7.98)	3.00 (2.00 - 5.00)
AUC_{8h}, ng.h/mL	12534 ± 6554	9632 ± 4293	8607 ± 2298
Day 6			
C_{0h}, ng/mL	2676 ± 836	2199 ± 843	1365 ± 267
C_{min}, ng/mL	2256 ± 688	1831 ± 696	1094 ± 184
C_{max}, ng/mL	3813 ± 1112	2898 ± 1024	2445 ± 481
t_{max}, h	4.00 (2.00 - 6.00)	3.25 (1.00 - 6.00)	2.50 (2.00 - 3.50)
AUC_{8h}, ng.h/mL	23849 ± 7199	18845 ± 7016	13628 ± 3090
C_{avg}, ng/mL	2981 ± 900	2353 ± 873	1704 ± 386
FI, %	52.9 ± 19.5	47.0 ± 13.9	78.3 ± 6.32
CL/F, L/h	34.0 ± 9.38	44.7 ± 16.2	57.1 ± 12.5
$C_{max, Day 6/Day 1}$	1.40 ± 0.335	1.47 ± 0.300	1.33 ± 0.296
$AUC_{8h, Day 6/Day 1}$	2.15 ± 0.730	2.15 ± 0.867	1.61 ± 0.238
	GLS mean ratio (90% CI)		
	test vs reference		
N	10 vs 10		
Day 1			
C_{max}	0.71 (0.53 – 0.95)		
AUC_{8h}	0.78 (0.55 – 1.12)		
Day 6			
C_{max}	0.75 (0.59 – 0.95)		
AUC_{8h}	0.78 (0.60 – 1.00)		

Unbound telaprevir

The individual mean values of the unbound fractions of total telaprevir obtained at the various time points on Days 1 and 6 ranged between 0.212 and 0.381 for healthy control subjects, between 0.323 and 0.461 in subjects with moderate hepatic impairment, and between 0.324 and 0.455 in subjects with severe hepatic impairment.

A summary of key pharmacokinetic parameters of unbound telaprevir for all 3 groups and the statistical results comparing the plasma concentrations of unbound telaprevir between subjects with moderate hepatic impairment and healthy control subjects are presented in the table below:

Pharmacokinetics of unbound telaprevir[a] (mean ± SD)	**750 mg q8h telaprevir on Days 1 to 5 + morning dose of 750 mg telaprevir on Day 6 in healthy control subjects (reference)**	**750 mg q8h telaprevir on Days 1 to 5 + morning dose of 750 mg telaprevir on Day 6 in subjects with moderate hepatic impairment (test)**	**750 mg q8h telaprevir on Days 1 to 5 + morning dose of 750 mg telaprevir on Day 6 in subjects with severe hepatic impairment**
N	10	10	4
Day 1			
C_{max}, ng/mL	872 ± 289	740 ± 268	721 ± 141
AUC_{8h}, ng.h/mL	3787 ± 1668	3527 ± 1454	3234 ± 431
Day 6			
C_{0h}, ng/mL	838 ± 275	748 ± 325	505 ± 32.4
C_{min}, ng/mL	746 ± 216	676 ± 215	428 ± 64.3
C_{max}, ng/mL	1244 ± 259	1070 ± 294	945 ± 61.0
AUC_{8h}, ng.h/mL	7826 ± 1978	6957 ± 2083	5257 ± 526
CL/F, L/h	101 ± 25.0	116 ± 32.1	144 ± 13.6
$C_{max,\ Day\ 6/Day\ 1}$	1.51 ± 0.375	1.50 ± 0.299	1.35 ± 0.271
$AUC_{8h,\ Day\ 6/Day\ 1}$	2.32 ± 0.880	2.19 ± 0.903	1.64 ± 0.217
	GLS mean ratio (90% CI)		
	test vs reference		
N	10 vs 10		
Day 1			
C_{1h}, ng/mL	2.36 (0.51 – 10.90)		
C_{4h}, ng/mL	0.78 (0.44 – 1.38)		
C_{8h}, ng/mL	1.06 (0.73 – 1.56)		
C_{max}, ng/mL	0.85 (0.66 – 1.09)		
AUC_{8h}, ng.h/mL	0.94 (0.67 – 1.31)		
Day 6			
C_{0h}, ng/mL	0.85 (0.62 – 1.18)		
C_{1h}, ng/mL	0.93 (0.72 – 1.19)		
C_{4h}, ng/mL	0.83 (0.67 – 1.03)		
C_{8h}, ng/mL	0.94 (0.74 – 1.20)		
C_{max}, ng/mL	0.85 (0.71 – 1.02)		
AUC_{8h}, ng.h/mL	0.88 (0.72 – 1.09)		

[a] For each subject, unbound C_{max}, C_{min}, and AUC_{8h} was calculated by multiplying the respective value for total telaprevir and the mean of the reported unbound fractions at predose and 1h, 4h, and 8h postdose. Unbound C_{0h} C_{1h}, C_{4h},and C_{8h} were calculated using the respective value for total telaprevir and the reported unbound fraction at the corresponding time point. Unbound CL/F on Day 6 was calculated by dividing the value for total telaprevir by the mean fraction unbound on Day 6.

From visual inspection of the scatter plots showing individual values of C_{max} and AUC_{8h} versus individual values of measures of hepatic function, no clear relationship was observed between C_{max} or AUC_{8h} values for total or free telaprevir values and albumin, bilirubin, and PT, both on Days 1 and 6 of treatment with telaprevir at 750 mg q8h. For AAG, individual values of C_{max} and AUC_{8h} for total and free telaprevir appear to be positively correlated with AAG values on Days 1 and 6.

SAFETY RESULTS:

No deaths or SAEs occurred during the study and none of the subjects discontinued the study drug due to an AE. One subject interrupted study drug intake due to an AE (head injury; the subject did not take the 3 doses of study drug on Day 3).

Apart from Grade 3 head injury in one subject, all AEs were Grade 1 or 2 in severity.

Four (40.0%) moderate hepatic impaired subjects experienced AEs during the treatment period. The most frequently reported AE was diarrhea, in 2 (20.0%) subjects. None of the other AEs were reported in more than 1 (10.0%) moderate hepatic impaired subject.

Half (5 subjects, 50.0%) of the healthy control subjects experienced AEs during the treatment period. The most frequently reported AE was proctalgia, in 2 (20.0%) subjects. None of the other AEs were reported in more than 1 (10.0%) healthy control subject.

Apart from one (25.0%) severe hepatic impaired subject who had progression of ascites observed at screening to Grade 2 in severity at follow-up, none of the severe hepatic impaired subjects had AEs during the study.

None of the AEs reported during the study were considered related to the study drug by the investigator, and incidences of AEs that were considered possibly related were low: 2 (20.0%) moderate hepatic impaired subjects each had 2 AEs that were considered to be possibly related to the study drug by the investigator (pollakiuria and diarrhea in one subject and hyperuricemia and blood creatinine increased in one subject) and 4 (40.0%) healthy control subjects had AEs that were considered to be possibly related to the study drug by the investigator (proctalgia in two healthy control subjects and anal pruritus and headache each in one healthy control subject).

Treatment-emergent graded laboratory abnormalities were observed in at most 2 subjects per subject group (i.e., 20.0% of moderate hepatic impaired subjects and healthy control subjects and 50.0% of severe hepatic impaired subjects). They were at most Grade 2, apart from Grade 3 absolute lymphocyte count decreased, hemoglobin decreased, and hyperuricemia in 1 (10.0%) moderate hepatic impaired subject and Grade 4 hyperbilirubinemia (total bilirubin increased) in 1 (25.0%) severe hepatic impaired subject. Laboratory-related AEs were reported in one subject in the study (moderate hepatic impaired subject; Grade 2 hyperuricemia and blood creatinine increased).

Incidences of ECG abnormalities were low in all 3 subject groups. None of the subjects had QTcF >480 ms or increase in QTcF from reference >60 ms. None of the ECG abnormalities were reported as AE.

Incidences of vital sign abnormalities were low in all 3 subject groups. None of the vital sign abnormalities were reported as AE.

The safety observations from this study indicated a similar tolerability of telaprevir in the 3 groups included in the study.

STUDY LIMITATIONS:

As the comparison of pharmacokinetic parameters in subjects with severe hepatic impairment (Group 3) and normal hepatic function (Group 2) was exploratory, subjects with severe hepatic impairment and

normal hepatic function were not matched and a low number of subjects with severe hepatic impairment was enrolled (N=4).

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