SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	To be determined
Name of Active Ingredient	TMC647055

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Status: Approved

Date: 23 September 2013

Prepared by: Janssen Infectious Diseases - Diagnostics BVBA

Protocol No.: TMC647055HPC1005

Title of Study: A Phase 1, open-label trial in genotype 1 HCV infected subjects to determine the safety, tolerability, pharmacokinetics, and antiviral activity of repeated doses of TMC647055 given in combination with telaprevir

Study Name: TMC647055HPC1005

EudraCT Number: 2011-004028-37

NCT No.: NCT01582035

Clinical Registry No.: CR100735

Principal Investigator: Markus Uhle, Charite Research Organisation, Chariteplatz 1, 10117, Berlin, Germany

Study Centers: The study was conducted in 3 centers in Germany.

Publication (Reference): None

Study Period: Study ongoing; date study initiated: 2 May 2012; cut-off date for the primary analysis: 3 June 2013

Phase of Development: 1

Objectives: The objectives of the study were:

- To determine the plasma pharmacokinetics, safety, and tolerability of 10 days combination therapy (TMC647055 at 500 mg twice daily [bid] and telaprevir at a dose of 1,125 mg bid [Panel 1]) or 14 days combination therapy (TMC647055 at 250 mg bid and telaprevir at a dose of 1,125 mg bid [Panel 1]) and 10 or 14 days combination therapy (TMC647055 at a dose up to 1,000 mg bid and telaprevir at a dose of 1,125 mg or 1,500 mg bid [Panel 2]) in chronic hepatitis C virus (HCV) genotype 1 infected subjects. The results of the short-term combination therapy were to be compared with historical data of TMC647055 from the 6 days monotherapy part in HCV-infected subjects in the TMC647055HPC1001 study.

- To study the antiviral activity of 10 days combination therapy (TMC647055 at 500 mg bid and telaprevir at a dose of 1,125 mg bid [Panel 1]) or 14 days combination therapy (TMC647055 at 250 mg bid and telaprevir at a dose of 1,125 mg bid [Panel 1]) and 10 or 14 days combination therapy (TMC647055 at a dose up to 1,000 mg bid and telaprevir at a dose of 1,125 mg or 1,500 mg bid [Panel 2]) in chronic HCV genotype 1 infected subjects. The results of the short-term combination therapy were to be compared with historical data of TMC647055 from the 6 days monotherapy part in HCV-infected subjects in the TMC647055HPC1001 study.

The Combination Therapy Phase was followed by an Extension Phase, in which telaprevir + pegylated inferferon (PegIFN)/ ribavirin (RBV) was to be provided. The objective of this extension was to provide access to an established therapy for subjects in Panel 1 and Panel 2, and describe the long-term safety of this regimen assessed by serious adverse events (SAEs) and adverse events (AEs) leading to discontinuation. HCV ribonucleic acid (RNA) levels and viral genome sequencing data were to be reported to the investigators for each subject; however, no formal evaluation of these parameters was to be undertaken.

Hypothesis

This was an exploratory study to investigate coadministration of TMC647055 and telaprevir that could result in an enhanced antiviral activity in HCV-infected subjects compared to intake of TMC647055 alone.

Methodology: This was an open-label study with a sequential design that consisted of a telaprevir + TMC647055 Combination Therapy Phase followed by an Extension Phase that included a 12-week follow-up period.

The study population consisted of genotype 1 chronic HCV-infected subjects, prior relapsers to interferon/RBV or pegIFN/RBV treatment, or treatment-naïve subjects. A total of 16 subjects were to be selected and divided over 2 panels (8 in each panel). All subjects had to have genotype 1 chronic hepatitis C (CHC) infection. Of the 8 subjects enrolled in each panel, maximum 2 were allowed to be of genotype 1b HCV infection and the remaining subjects had to have chronic HCV genotype 1a infection. Subjects who were enrolled after the second protocol amendment dated 1 October 2012 had to have chronic HCV genotype 1a infection.

Panel 1: Subjects enrolled before the second protocol amendment received TMC647055/telaprevir for 10 consecutive days. TMC647055 was administered at a dose of 500 mg bid and telaprevir at a dose of 1,125 mg bid. Subjects enrolled after the second protocol amendment received TMC647055/telaprevir for 14 consecutive days. TMC647055 was administered at a dose of 250 mg bid and telaprevir at a dose of 1,125 mg bid.

Panel 2: Subjects were to receive TMC647055/telaprevir for 10 or 14 consecutive days. Telaprevir was to be administered either at a dose of 1,125 or 1,500 mg bid. Dosage of TMC647055 could be adapted but could not be higher than 1,000 mg bid.

During the Combination Therapy Phase, the 2 panels were to be recruited sequentially. Dose level and dosing period of TMC647055, and dose level of telaprevir in Panel 2, were to be decided based on review of safety, tolerability, pharmacokinetics, and HCV RNA data of Panel 1. The Combination Therapy Phase for Panel 1 was initially 10 days and extended to 14 days after the second protocol amendment. Execution of Panel 2 was planned after data review of Panel 1. If Panel 2 was not executed, the Extension Phase for subjects enrolled in Panel 1 was to be continued.

In order to benefit maximally from the antiviral activity of the TMC647055/telaprevir combination therapy, subjects started the Extension Phase the day after completion of the combination therapy. Follow-up visits were not required for subjects prior to the initiation of Extension Phase. The Extension Phase treatment consisted of : 12 weeks of telaprevir (750 mg every 8 hours [q8h]) + PegIFNα-2a (180 µg subcutaneously [SC] once weekly) + RBV (1,000 or 1,200 mg/day [weight-based]) (Part 1), followed by

either 12 or 36 weeks of PegIFN/RBV therapy, based on HCV RNA response at Week 4 and Week 12 (Part 2). The first day of the Extension Phase corresponded to Day 11 or Day 15 following a Combination Therapy Phase of 10 days or 14 days, respectively.

Pharmacokinetic profiles of TMC647055 and telaprevir were evaluated during the Combination Therapy Phase. Safety and tolerability, HCV RNA kinetics (HCV RNA levels) and viral genome sequencing were also assessed during the Combination Therapy Phase, and in addition during the Extension Phase. Exploratory biomarkers at the mRNA, protein, and cell level could also be studied.

A mandatory assessment of genotyping of a single nucleotide polymorphism (rs12979860) upstream of the Interleukin 28B (IL28B) was done for each subject. Participation in additional host deoxyribonucleic acid (DNA) genotyping research was optional.

An interim database lock was performed when all subjects completed Day 11 (Combination Therapy Phase of 10 days) or Day 15 (Combination Therapy Phase of 14 days). In case of premature discontinuation, subjects had to complete the follow-up visits at Week 2 and Week 4 to evaluate the combination therapy data. This was the primary analysis evaluating the antiviral, pharmacokinetics and safety profile of the combination of TMC647055 and telaprevir. All data from subjects in Panels 1 and 2 (if applicable) were to be included. However, this analysis included data from Panel 1 only, as it was decided that Panel 2 would not be executed (for details, see below). The results are described in the present document. At the time of database lock for this analysis, most subjects were still ongoing in the Extension Phase of the study.

A second and final database lock will occur at the end of Week 12 follow-up visit when all subjects will have completed the Extension Phase or have discontinued earlier. The purpose of this analysis is to describe the long-term safety of this regimen assessed by the SAEs and AEs leading to discontinuation. HCV RNA levels and viral genome sequencing data will be investigated and results will be reported to the investigators for each subject, however, no formal evaluation of these parameters will be undertaken. Only data collected during the Extension Phase will be included in the analysis. The results will be described in an addendum to the present document.

Number of Subjects (planned and analyzed):

Planned: 16 subjects (8 subjects in each panel).

If selected subjects discontinued the study before receiving their first study drug dose, additional subjects had to be recruited to have 8 subjects starting treatment. If subjects were prematurely withdrawn from the study after starting treatment for reasons other than drug tolerability/safety, additional subjects had to be enrolled to ensure 8 evaluable subjects per panel.

Analyzed: 7 subjects (Panel 1).

Given the already extended time frame of the study and the existing environment of multiple long-term IFN-free combinations being evaluated in the field, it was decided that Panel 1 would be completed with the enrollment of 7 subjects (instead of the initially planned 8 subjects). Given the scientific advancement, it was also decided that Panel 2 would not be executed.

Diagnosis and Main Criteria for Inclusion:

Subjects had to be aged 18 to 60 years (extremes included) with documented chronic HCV genotype 1a or 1b HCV infection with HCV RNA level >100,000 IU/mL at screening (subjects enrolled in Panel 1 after Amendment 2 had to have HCV genotype 1a infection), prior relapsers or treatment-naïve, medically stable on the basis of physical examination, medical history, vital signs, 12-lead electrocardiogram (ECG), and laboratory tests recorded or performed at screening.

Subjects had to have a body mass index between 18 and 32 kg/m^2 (extremes included), and nonsmoking for at least 3 months prior to screening. Female subjects had to be postmenopausal or surgically sterile.

Subjects could not have evidence of liver cirrhosis; historical liver biopsy graded as advanced liver fibrosis (Metavir Score F>3) or evidence for the presence of oesophageal varices or a transient elastography (Fibroscan) result of more than 14.6 kPa within 3 years prior to first dosing or evidence of decompensated liver disease defined as prior history or current evidence of ascites, hepatic encephalopathy, bleeding oesophageal or gastric varices and/or any of the following screening laboratory results: international normalized ratio of ≥1.5; serum albumin <3.3 g/dL; serum total bilirubin ≥1.5 x upper limit of laboratory normal range (ULN).

Subjects could not have a history of seizure disorders, psychiatric condition, organ transplant requiring chronic immunosuppression, clinically significant retinopathy or ophthalmologic disorder including but not limited to disorders due to diabetes mellitus or hypertension, bacterial or fungal infections, acute or chronic pancreatitis, bleeding disorders, chronic pulmonary disease associated with functional impairment, congenital or acquired prolonged QT interval, medical condition that required chronic or intermittent use of systemic corticosteroids, any liver disease in addition to hepatitis C, hepatocellular carcinoma (HCC), human immunodeficiency virus (HIV)-1 or HIV-2, or hepatitis A or B virus infection.

Subjects could not have received any HCV treatment 6 months before screening, prior treatment with an HCV protease inhibitor and/or non-nucleoside inhibitor and/or NS5a inhibitor, and nonstable methadone. Subjects could not present a contraindication to the administration of PegIFNα-2a or RBV. Subjects with current abuse of alcohol, barbiturate, amphetamine, recreational, or narcotic drug use were excluded from the study.

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

TMC647055: Oral solution (25 mg/mL) at a dose of 500 mg bid for 10 days or 250 mg bid for 14 days in Panel 1 in the Combination Therapy Phase under fed conditions. TMC647055 dose for Panel 2 if executed, could be adapted, but could not be higher than 1,000 mg bid. Batch numbers: 11F20/G001, 11K28/G001, 11L01/G001, 11L15/G001, 12E31/G001.

Telaprevir: Formulation (F007), 1,125 mg bid given as 3 x 375-mg oral tablets under fed conditions for 10 or 14 days in Panel 1 in the Combination Therapy Phase: 1,125 mg (3 x 375-mg tablets) bid for 10 days or 1,500 mg (4 x 375-mg tablets) bid for 14 days in Panel 2, if executed. Telaprevir dose in the Extension Phase was to be 750 mg (2 x 375-mg tablets) q8h for 12 weeks. Batch numbers: BEL2N00, AGL3B00.

PegIFNα-2a (Pegasys®): Administered at a dose of 180 μg subcutaneously once a week for 24 or 48 weeks under fed conditions in the Extension Phase. Batch number: B1223.

RBV (Copegus®): 1,000 mg (<75 kg body weight) or 1,200 mg (≥75 kg body weight) given as 5 or 6 200-mg oral tablets daily in 2 divided doses under fed conditions for 24 or 48 weeks in the Extension Phase. Batch number: 899760.

Duration of Treatment: The duration of the Combination Therapy Phase was either 10 or 14 days. The Extension Phase was maximum 24 or 48 weeks (telaprevir treatment for 12 weeks followed by PegIFN/RBV therapy for either 12 or 36 weeks).

Criteria for Evaluation:

Pharmacokinetic evaluations:

The following pharmacokinetic parameters were derived for TMC647055 and telaprevir.

Combination Therapy Phase of 10 days: Panel 1 (Panel 2 if applicable)

- On Day 1: C_{12h}, C_{max}, t_{max}, $AUC_{12h.}$
- On Days 2 to 5 and on Days 7 to 9: $C_{trough.}$
- On Day 6: C_{trough}, $C_{12h,}$ C_{min}, C_{max}, t_{max}, AUC_{12h}, C_{avg}, fluctuation index (FI).
- On Day 10: C_{trough}, $C_{12h,}$ C_{min}, C_{max}, t_{max}, AUC_{12h}, C_{avg}, FI, Ratio $C_{12h\ Day\ 10/Day\ 1,}$ Ratio $C_{max\ Day\ 10/Day\ 1}$, Ratio $AUC_{12h\ Day\ 10/Day\ 1.}$

Combination Therapy Phase of 14 days: Panel 1 (Panel 2 if applicable)

- On Day 1: $C_{12h,}$ C_{max}, t_{max}, $AUC_{12h.}$
- On Days 2 to 5 and on Days 7-13: $C_{trough.}$
- On Day 6: C_{trough}, C_{12h}, C_{min}, C_{max}, t_{max}, AUC_{12h}, C_{avg}, FI.
- On Day 14: C_{trough}, $C_{12h,}$ C_{min}, C_{max}, t_{max}, AUC_{12h}, C_{avg}, FI, Ratio $C_{12h\ Day\ 14/Day\ 1,}$ Ratio $C_{max\ Day\ 14/Day\ 1}$, Ratio $AUC_{12h\ Day\ 14/Day\ 1.}$

Safety evaluations:

AEs: AEs were collected throughout the study from signing of the informed consent form onwards until the safety follow-up visit scheduled 4 weeks after last intake of study drugs. Thereafter, only SAEs (regardless of causality) were to be reported until the subject's final study visit.

Laboratory Safety: Blood samples for serum chemistry and hematology, and a random urine sample for urinalysis were collected. The subjects had to fast for at least 10 hours (Panels 1 and 2) or 7 hours (Extension Phase) before the safety blood sample was taken. In case of dropout, subjects were not required to fast for 10 hours (Panels 1 and 2) or 7 hours (Extension Phase) before the safety blood sample was taken at the time of dropout.

ECG: Twelve-lead ECGs were recorded and ECG measurements were to be performed in triplicate on all time points scheduled in Panel 1 and Panel 2 (if executed). During the Extension Phase single ECGs were to be performed. The QT-intervals were corrected for heart rate according to Bazett's (QTcB) or Fridericia's (QTcF).

Vital Signs: Systolic and diastolic blood pressure, and pulse rate (supine after at least 5 minutes rest; standing after at least 1 minute standing) were recorded.

Physical Examination: Physical examination (including skin examination) was performed at screening and at several time points throughout the study.

Liver Ultrasound: An ultrasound of the liver had to be performed between screening and baseline visit to assess for findings suspicious for HCC, if the alpha-fetoprotein level at screening was >50 ng/mL.

Antiviral Activity: Samples for the determination of HCV RNA levels were taken at specified time points. Plasma HCV RNA levels were determined using an in vitro nucleic acid amplification test for the quantification of HCV RNA in human plasma. The changes in HCV RNA levels, including viral breakthrough and incomplete virologic suppression, were evaluated by the sponsor virologist.

Viral Sequencing: Sequencing of the NS5B and NS3/4a region could be performed to monitor HCV variants present at scheduled time points. The NS3/4a and NS5B region was sequenced in the baseline sample for all subjects. The sequencing of the NS3/4a and NS5B region in the other samples could be triggered by the sponsor virologist based on the changes in HCV RNA levels observed in each individual subject and the limits of the sequencing assay. Additionally, phenotypic analysis could be performed on selected samples, including samples carrying mutations not previously characterized. The results of phenotype changes were evaluated by the sponsor virologist. Changes in the viral sequence or phenotype were not reported as AEs or SAEs.

Samples could be used by the sponsor for additional assessments analyzing the genotypic and phenotypic characteristics of the HCV present in these samples. In case viral sequencing was required and no dedicated sample was taken at that time point, leftover HCV RNA samples could be used if available.

Host Pharmacogenomic Testing:

IL28B Genotyping: 1 sample for *IL28B* genotyping was collected from all subjects, preferably at baseline.

Host DNA Genotyping Research: For subjects who gave a separate informed consent, an additional blood sample was collected, preferably at baseline, for research on host DNA genotyping.

Biomarker Research: The study included the option for analyzing exploratory biomarkers at the mRNA, protein, and cell level, as these markers could play a role in the level of treatment response.

Statistical Methods:

The present primary analysis was performed on the data of Panel 1 only (Combination Therapy Phase data).

Statistical methods used in the study were descriptive statistics, linear mixed effects modeling, graphical analysis, intent-to-treat.

RESULTS:

Focus in this document is on the data from the Combination Therapy Phase. Data from the Extension Phase available in the database at the time of database lock are not described (unless otherwise specified).

STUDY POPULATION:

Of 16 subjects screened, 7 chronic HCV-infected subjects (5 treatment-naïve and 2 prior relapsers; 6 had genotype 1a and 1 had genotype 1b infection) were enrolled in Panel 1 and treated. Five subjects were enrolled before Amendment 2 and received TMC647055 at a dose of 500 mg bid in combination with telaprevir at a dose of 1,125 mg bid for 10 consecutive days. Two subjects were enrolled after Amendment 2 and received TMC647055 at a dose of 250 mg bid and telaprevir at a dose of 1,125 mg bid for 14 consecutive days.

All subjects in Panel 1 completed the Combination Therapy Phase and continued in the Extension Phase. No subjects prematurely discontinued the study. At the time of database lock for the present analysis, 2 subjects had completed the study and 5 subjects were still continuing in the Extension Phase (3 subjects in Part 1 and 2 subjects in Part 2).

Demographic Parameters	T + TMC647055
Analysis set: intent-to-treat	7
Age (years)	
Mean (SD)	46.6 (6.11)
Median (Range)	48.0 (37; 54)
Height (cm)	
Mean (SD)	177.9 (11.68)
Median (Range)	182.0 (158; 190)
Weight (kg)	
Mean (SD)	79.6 (16.86)
Median (Range)	81.0 (54; 104)
BMI (kg/m²)	
Mean (SD)	24.93 (3.362)
Median (Range)	25.70 (20.2; 30.4)
Sex, n (%)	
Female	1 (14.3%)
Male	6 (85.7%)

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

Baseline Characteristics	T + TMC647055
Analysis set: intent-to-treat	7
HCV RNA (IU/mL)[a]	
Mean (SD)	4917142.9 (6849774.85)
Median (Range)	2260000.0 (135000; 19600000)
Log_{10} HCV RNA[a]	
Mean (SD)	6.309 (0.6991)
Median (Range)	6.354 (5.13; 7.29)
HCV genotype, n (%)	
1a	6 (85.7%)
1b	1 (14.3%)
IL28B genotyping, n (%)	
CC	2 (28.6%)
CT	3 (42.9%)
TT	2 (28.6%)
Metavir score, n (%)	
F1	1 (14.3%)
F2	1 (14.3%)
Nav	5 (71.4%)

n: number of subjects with that observation; NAv: not available
[a] screening values

PHARMACOKINETIC RESULTS:

For TMC647055 in combination with telaprevir for the 10-day combination therapy (TMC647055 at 500 mg bid + telaprevir at 1,125 mg bid), mean C_{12h}, C_{max}, and AUC_{12h} were higher on Day 6 compared to Day 1. On the last day of treatment (Day 10), C_{max} and AUC_{12h} were lower than on Day 6 but higher than on Day 1, while C_{12h} on the last day of treatment (Day 10) was lower than on Days 1 and 6. For the 2 subjects who received TMC647055 at 250 mg bid for 14 days, see the table on page 9.

For the 5 subjects receiving the 10-day combination therapy, geometric mean values of the Day 10/Day 1 accumulation ratios for C_{12h}, C_{max}, and AUC_{12h} of TMC647055 were 60%, 121%, and 123%, respectively. For the 2 subjects receiving the 14-day combination therapy, individual Day 14/Day 1 ratios for these parameters were 106% and 50%, 126% and 101%, and 108% and 119%, respectively. For the 2 subjects who received 14-day combination therapy, see the table on page 9.

After intake of TMC647055 in the presence of telaprevir in the current study, C_{min}, C_{max}, and AUC_{12h} of TMC647055 were, respectively, 12-fold, 3.3-fold and 5.9-fold higher, compared to after intake of TMC647055 alone (data from study TMC647055HPC1001 as historical control), based on the ratios of the least square (LS) means, in HCV-infected subjects. The corresponding 90%CIs were wide.

For telaprevir in combination with TMC647055 for the 10-day combination therapy, based upon the mean values, C_{12h} and C_{max} were comparable on Day 6 and on the last day of treatment. On Day 1, higher C_{12h} and C_{max} values were observed. AUC_{12h} of telaprevir was generally comparable on these days. For the 2 subjects who received 14-day combination therapy, see the table on page 10.

For the 5 subjects receiving the 10-day combination therapy, geometric mean values of the Day 10/Day 1 accumulation ratios for C_{12h}, C_{max}, and AUC_{12h} of telaprevir were 67%, 88%, and 108%, respectively. For the 2 subjects receiving the 14-day combination therapy, individual Day 14/Day 1 ratios for these parameters were 58% and 63%, 84% and 70%, and 65% and 89%, respectively.

For telaprevir, C_{trough}, C_{min}, C_{12h}, C_{max}, C_{avg}, and AUC_{12h} values for the 14-day combination therapy (telaprevir at 1,125 mg bid + TMC647055 at 250 mg bid) were in range with the mean values of these parameters for the 10-day combination therapy (telaprevir at 1,125 mg bid + TMC647055 at 500 mg bid), on all days of treatment, as applicable.

Pharmacokinetics of TMC647055 (Mean ± SD, t_{max}: Median [Range])	**TMC647055 at 500 mg bid + Telaprevir at 1,125 mg bid on Days 1 to 10**	**TMC647055 at 250 mg bid + Telaprevir at 1,125 mg bid on Days 1 to 14**
N	5	2[a]
Day 1		
C_{12h}, ng/mL	4840±3046	2260-3210
C_{max}, ng/mL	13442±5056	5860-12500
t_{max}, h	4.00 (2.02-5.02)	4.00-4.00
AUC_{12h}, ng.h/mL	95198±46566	33844-78852
Day 6		
C_{trough}, ng/mL	7942±5996	2910-5400
C_{12h}, ng/mL	5520±5118	2290-5310
C_{min}, ng/mL	5520±5118	2290-4150
C_{max}, ng/mL	22660±8652	8680-14600
t_{max}, h	4.03 (3.97-5.00)	3.95-5.03
AUC_{12h}, ng.h/mL	164983±91396	57663-104456
C_{avg}, ng/mL	13763±7604	4817-8741
FI, %	141±43.6	120-133
Day 10/Day 14		
C_{trough}, ng/mL	3630±1215	1390-4160
C_{12h}, ng/mL	2766±1716	1130-3400
C_{min}, ng/mL	2712±1599	1130-3090
C_{max}, ng/mL	15620±3885	5900-15800
t_{max}, h	4.00 (1.98-4.03)	3.97-4.00
AUC_{12h}, ng.h/mL	108669±27696	40157-85237
C_{avg}, ng/mL	9067±2306	3341-7133
FI, %	145±13.6	143-178

[a] Individual values (N=2)

Pharmacokinetics of Telaprevir (Mean ± SD, t_{max}: Median [Range])	**Telaprevir at 1,125 mg bid + TMC647055 at 500 mg bid on Days 1 to 10**	**Telaprevir at 1,125 mg bid + TMC647055 at 250 mg bid on Days 1 to 14**
N	5	2[a]
Day 1		
C_{12h}, ng/mL	1561±747	1360-2020
C_{max}, ng/mL	3778±1689	4040-4470
t_{max}, h	5.07 (4.02 - 6.12)	4.02 - 5.05
AUC_{12h}, ng.h/mL	24899±11308	23248-35214
Day 6		
C_{trough}, ng/mL	2137±953	2340-2450
C_{12h}, ng/mL	1123±399	1800-1870
C_{min}, ng/mL	1123±399	1800-1870
C_{max}, ng/mL	3230±677	3140-4600
t_{max}, h	4.12 (2.00 - 5.00)	5.03 - 5.05
AUC_{12h}, ng.h/mL	24953±6386	27768-31972
C_{avg}, ng/mL	2076±528	2314-2671
FI, %	104±19.2	57.9-102
Day 10/Day 14		
C_{trough}, ng/mL	1596±485	1700-1940
C_{12h}, ng/mL	982±344	850-1170
C_{min}, ng/mL	982±344	850-1170
C_{max}, ng/mL	3100±902	2840-3770
t_{max}, h	5.00 (4.03 - 5.02)	3.98 - 5.03
AUC_{12h}, ng.h/mL	24243±4450	20702-22996
C_{avg}, ng/mL	2020±371	1721-1920
FI, %	103±29.6	116-135

[a] Individual values (N=2)

SAFETY RESULTS:

Adverse Events

There were no deaths, other SAEs, or AEs leading to permanent or temporary discontinuation of the study drugs during the study.

All subjects experienced at least 1 AE during the Combination Therapy Phase. The most frequently observed AEs (in more than 2 subjects) were anorectal discomfort (4 subjects), headache (3 subjects), and pruritus (3 subjects). The majority of AEs during the Combination Therapy Phase were grade 1 in severity. One subject had grade 2 AEs (2 occurrences of headache, and rash). There were no grade 3 or 4 AEs.

AEs were considered by the investigator to be at least possibly related to TMC647055 in 6 subjects, and to telaprevir in 7 subjects. The most common drug-related AEs were anorectal discomfort and pruritus. One grade 2 AE (rash) was considered at least possibly related to both TMC647055 and telaprevir.

One subject experienced a skin event of interest during the Combination Therapy Phase (grade 1 and grade 2 rash).

Clinical Laboratory Tests

There were no consistent or clinically relevant changes over time in median laboratory values. Except for 1 subject with a grade 3 increase in gamma glutamyl transferase, all graded laboratory abnormalities during the Combination Therapy Phase were grade 1 or grade 2 in severity. Nongraded laboratory abnormalities occurring in more than 1 subject during the Combination Therapy Phase were decreased erythrocytes mean corpuscular hemoglobin concentration and increased erythrocytes mean corpuscular volume. No laboratory abnormalities were reported as an AE during the Combination Therapy Phase.

Other Safety Observations

Median changes in ECG parameters and vital signs were generally small, and none of them were considered clinically relevant. No subjects had a QTcF value above 450 ms. One subject had a QTcB value between 450 and 480 ms and 1 subject had an abnormally high PR interval value. No subjects had an increase in QTcB or QTcF of 30 ms or more. One vital signs abnormality was grade 2 in severity (increase in standing DBP). No ECG or vital signs abnormalities were reported as AEs during the Combination Therapy Phase.

There were no clinically relevant abnormal findings during physical examination during the Combination Therapy Phase.

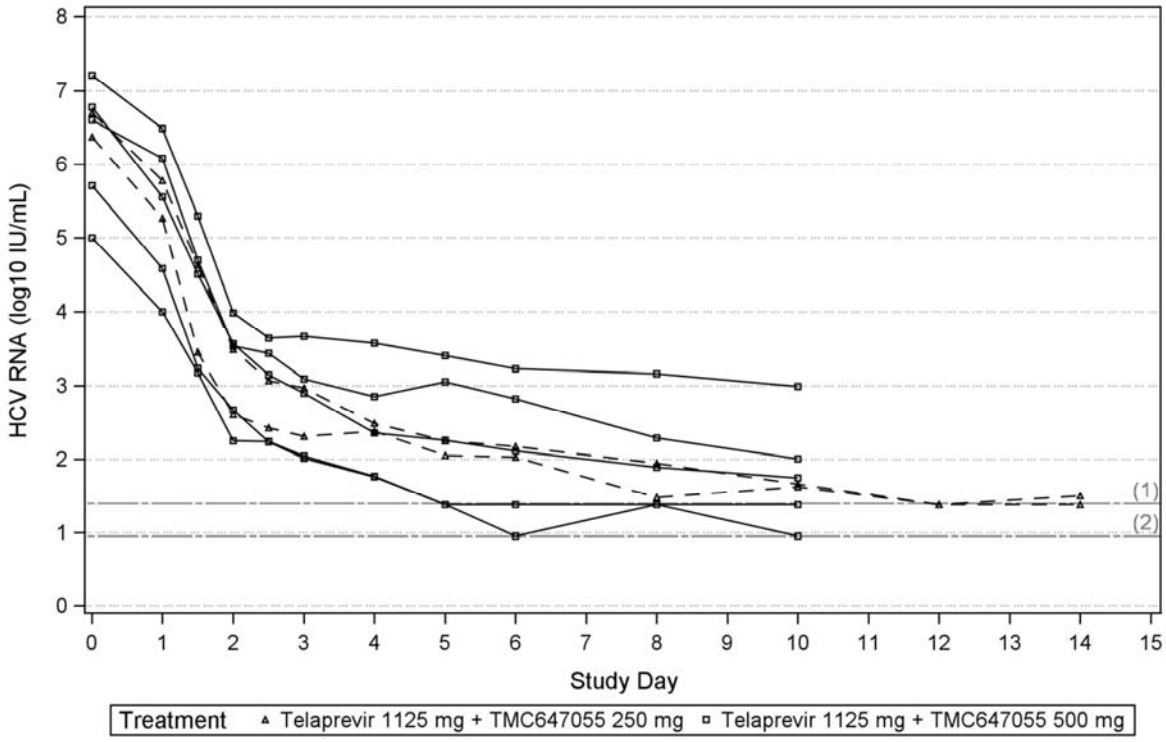
ANTIVIRAL ACTIVITY

A potent antiviral activity was observed in 5 subjects who received TMC647055 500 mg bid combined with telaprevir 1,125 mg bid for 10 days, with a median maximum decrease from baseline (Day 1) in HCV RNA of 4.33 $\log_{10}$ IU/mL. By Day 4, all 5 subjects had a decrease from baseline in HCV RNA of >3 $\log_{10}$ IU/mL. Two of the 5 subjects (both genotype 1a) had HCV RNA levels <25 IU/mL detectable on Day 5. For 1 of these 2 subjects, HCV RNA remained <25 IU/mL detectable until Day 10, and for the other subject after Day 5 HCV RNA levels alternated between <25 IU/mL detectable and undetectable, resulting in undetectable at Day 10. In the other 3 subjects (2 genotype 1a and 1 genotype 1b), HCV RNA levels at Day 10 were, respectively, 56 IU/mL, 101 IU/mL, and 983 IU/mL (the last value occurred in the genotype 1b subject with the highest baseline HCV RNA levels, but for whom a similar maximum decrease from baseline in HCV RNA [4.22 $\log_{10}$ IU/mL] was observed as for the other subjects).

A potent antiviral activity was also observed in 2 subjects who received TMC647055 250 mg bid combined with telaprevir 1,125 mg bid for 14 days, with maximum decreases from baseline in HCV RNA of 5.00 and 5.32 $\log_{10}$ IU/mL. By Day 4, both subjects had a decrease from baseline in HCV RNA of ≥4 $\log_{10}$ IU/mL. HCV RNA first reached <25 IU/mL detectable on Day 12 in both subjects and remained <25 IU/mL detectable until Day 14 in 1 subject, while in the other subject an HCV RNA level of 32 IU/mL was observed on Day 14.

No viral breakthroughs were observed.

Individual Plasma HCV RNA (log_{10} IU/mL) Values Over Time



1) HCV RNA < 25 IU/mL detectable
2) HCV RNA < 25 IU/mL undetectable

Compared to the TMC647055 monotherapy data from Panel 7 (dosing with 500 mg bid) in the HPC1001 study, the combination of TMC647055 and telaprevir showed a more potent antiviral activity with a larger median maximum decrease from baseline in HCV RNA (4.33 log_{10} IU/mL in HPC1005 versus 1.46 log_{10} IU/mL in HPC1001), a continuous suppression of HCV RNA levels during the dosing, and the ability to achieve HCV RNA levels below 25 IU/mL (detectable or undetectable) in 4 subjects during or at the end of dosing (not observed in HPC1001).

VIRAL SEQUENCING

No polymorphisms associated with reduced susceptibility in vitro to telaprevir or TMC647055 were observed at baseline and no emerging mutations associated with in vitro reduced susceptibility to telaprevir or TMC647055 were detected during dosing. In 1 genotype 1a subject, 3 mutations in the NS3/4a protease (Q80L, T98S, and S122G) that have not been identified as telaprevir-resistant variants in the telaprevir Phase 2 and 3 studies were detected at Days 2, 3, and 4 of dosing (no NS3/4a sequencing information was available at later time points).

STUDY LIMITATIONS:

Given the already extended time frame of the study and the existing environment of multiple long-term IFN-free combinations being evaluated in the field, it was decided that Panel 1 would be completed with the enrollment of 7 subjects (instead of the initially planned 8 subjects). Given the scientific advancement, it was also decided that Panel 2 would not be executed.

CONCLUSIONS:

The results of this study demonstrate that C_{12h}, C_{max}, and AUC_{12h} for TMC647055 at 500 mg bid, administered in combination with telaprevir for 10 days (N=5) were higher on Day 6 compared to Day 1. On Day 10, mean C_{max} and AUC_{12h} were lower than on Day 6 but higher than on Day 1, while mean C_{12h} was lower than on Days 1 and 6. The Day 10 C_{min}, $C_{max,}$ and AUC_{12h} values of TMC647055 in the current study were, respectively, 12-fold, 3.3-fold, and 5.9-fold higher, compared to after intake of TMC647055 at 500 mg bid alone (historical control, TMC647055HPC1001, Day 6), based on the ratios of the LS means. For the 2 subjects who received TMC647055 at 250 mg bid for 14 days, also in combination with telaprevir, the same trend in TMC647055 AUC_{12h} on Days 1, 6, and 14 was observed as for Days 1, 6, and 10 in the 10-day combination therapy.

For telaprevir, administered in combination with TMC647055, C_{12h} and C_{max} were generally comparable on Day 6 and on the last day of treatment, while on Day 1 slightly higher values were observed. AUC_{12h} of telapevir was generally comparable on these days.

The administration of TMC647055 500 or 250 mg bid in combination with telaprevir 1,125 mg bid for 10 or 14 days was generally safe and well tolerated in chronic genotype 1 HCV-infected subjects. There were no new safety findings compared to TMC647055 administered alone.

Compared to TMC647055 monotherapy, the combination of TMC647055 and telaprevir substantially increased the antiviral activity in chronic genotype 1 HCV-infected subjects. A continuous suppression of HCV RNA levels was obtained during dosing and in 4 subjects HCV RNA was below 25 IU/mL (detectable or undetectable) during or at the end of dosing.

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