SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development**
Name of Investigational Product	TMC435 (simeprevir)

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Status: Approved

Date: 26 November 2015

Prepared by: Janssen Infectious Diseases - Diagnostics BVBA

Protocol No.: TMC435-TiDP16-C213

Title of Study: A Phase 3, Open-label Trial of TMC435 in Combination With Peginterferon α-2a and Ribavirin for HCV Genotype 1 Infected Subjects who Participated in the Placebo Group of a Phase 2/3 TMC435 Study (C201, C205, C206, C208, C216 or HPC3007), or who Received Short-term (up to 14 Days) Direct-acting Antiviral Treatment for Hepatitis C Infection in a Selected Tibotec*-sponsored Phase 1 Study

*Now called Janssen Research & Development (JRD); in the remainder of the synopsis, Tibotec will be replaced by JRD.

Study Name: TMC435-TiDP16-C213

EudraCT Number: 2011-000416-25

NCT No.: NCT01323244

Clinical Registry No.: CR017983

Coordinating Investigator: Ed Gane, MD

Study Center(s): Subjects were screened and treated at 75 sites in 22 countries: Australia (4 sites), New Zealand (2 sites), Austria (2 sites), Belgium (4 sites), Bulgaria (1 site), Germany (7 sites), Spain (3 sites), France (4 sites), United Kingdom (2 sites), Iceland (2 sites), Italy (1 site), The Netherlands (2 sites), Poland (5 sites), Portugal (3 sites), Romania (1 site), Russian Federation (8 sites), Ukraine (3 sites), Canada (3 sites), Mexico (1 site), United States (14 sites), Argentina (2 sites), Brazil (1 site).

Publication (Reference): Gane E, George J, Ferenci P, et al. Simeprevir with peginterferon/ribavirin for treatment of chronic hepatitis C virus genotype 1 infection in treatment-experienced patients: interim results of a phase III rollover trial. Hepatol Int. 2014; 8: S130-S131.

Study Period: 5 December 2011 to 31 March 2015

Phase of Development: 3

Objectives:

The study aimed to provide access to simeprevir (SMV) treatment in combination with pegylated interferon alpha-2a/ribavirin (PegIFNα-2a/RBV) and to evaluate the efficacy and safety of SMV in the following treatment-experienced subjects: (1) subjects who had participated in the placebo group of a

Phase 2/3 SMV study and who did not achieve sustained viral response 12 or 24 weeks (SVR12 or SVR24) after the planned end of treatment (EOT) (Phase 2/3 group), and (2) subjects who had received short-term (up to 14 days) direct-acting antiviral agent (DAA) treatment for hepatitis C virus (HCV) infection in the selected JRD-sponsored Phase 1 studies (Phase 1 group). All efficacy-related objectives below were to be investigated separately in the Phase 2/3 and Phase 1 groups. Data from the Phase 2/3 group were to be analyzed overall and by subgroup depending on their treatment response in the previous SMV study (subjects with viral relapse, viral breakthrough, and nonresponse, ie, null response, partial response, and non-classifiable nonresponse ['others']). The safety-related objectives were investigated in the overall population.

The primary objective was to evaluate the efficacy of SMV in combination with PegIFNα-2a and RBV, with respect to the proportion of subjects with SVR12 (1) in the Phase 2/3 group and (2) in the Phase 1 group.

The secondary objectives were:

- To evaluate the efficacy of SMV in combination with PegIFNα-2a and RBV with respect to the proportion of subjects with SVR24.
- To evaluate the antiviral activity to SMV in combination with PegIFNα-2a and RBV at all time points, with focus on Week 4, Week 12, Week 24 and Week 48.
- To evaluate the incidence of on-treatment failure.
- To evaluate the rate of HCV viral breakthrough during treatment.
- To evaluate the viral relapse rate after treatment.
- To determine the proportion of subjects who meet the criteria for treatment completion at Week 24 in the subgroups of subjects who had experienced viral relapse or viral breakthrough in a Phase 2/3 SMV study.
- To determine the viral non-structured protein (NS) 3/4A sequence in subjects not achieving SVR.
- To evaluate the safety and tolerability of SMV in combination with PegIFNα-2a and RBV.

Methodology: This was an open-label study of SMV in combination with PegIFNα-2a and RBV for subjects with HCV genotype 1 infection who had participated in the placebo group of a Phase 2/3 SMV study, or who had received short-term (up to 14 days) DAA treatment for HCV infection in the selected JRD-sponsored Phase 1 studies. The efficacy of SMV in combination with PegIFNα-2a and RBV in adult subjects was evaluated separately for the 2 groups of subjects (previously Phase 2/3 or Phase 1, respectively). Safety and tolerability were evaluated in the overall population.

Subjects in the Phase 2/3 group were classified by the sponsor as (1) subjects with viral relapse, (2) subjects with viral breakthrough, or (3) nonresponders, ie, null responders, partial responders, and non-classifiable nonresponders, based on their response to PegIFNα-2a (2b)/RBV therapy in the feeder study. Subjects could only enter the study after completion of the last study-related visit in the previous study.

The present study included a screening period of up to 6 weeks. Only under exceptional circumstances and after sponsor approval, the 6-week period could be exceeded.

This report describes the results of the primary analysis, which was also the final analysis, and includes data up to the date of last subject last visit, 31 March 2015, when all enrolled subjects had completed the last study-related visit (Week 48 or Week 72) or discontinued earlier.

All subjects were to receive 12 weeks of treatment with SMV 150 mg once daily (qd) in combination with PegIFNα-2a 180 µg once weekly and RBV 1,000-1,200 mg per day (twice daily regimen, weight based).

A response-guided treatment (RGT) duration of 24 or 48 weeks with PegIFNα-2a/RBV was used for subjects in the Phase 2/3 group who had experienced viral relapse or viral breakthrough in the feeder study. To determine the total treatment duration with PegIFNα-2a/RBV (24 or 48 weeks), HCV ribonucleic acid (RNA) plasma levels had to be assessed at Weeks 4 and 12 of treatment. The Original Treatment Duration Guidelines (OTDGs) applied to subjects enrolled prior to protocol amendment IV were as follows:

- If HCV RNA <25 IU/mL (detectable or undetectable) at Week 4 and HCV RNA <25 IU/mL undetectable at Week 12: Subjects were to receive PegIFNα-2a/RBV for a total treatment duration of 24 weeks (ie, 12 weeks of treatment with SMV + PegIFNα-2a/RBV, followed by 12 weeks of treatment with PegIFNα-2a/RBV).
- If the above criteria were not met: Subjects were to receive PegIFNα-2a/RBV for a total treatment duration of 48 weeks (ie, 12 weeks of treatment with SMV + PegIFNα-2a/RBV, followed by 36 weeks of treatment with PegIFNα-2a/RBV).

The Modified Treatment Duration Guidelines (MTDGs) applied to subjects enrolled under Amendment IV or later amendments were as follows:

- If HCV RNA <25 IU/mL undetectable at Week 4: Subjects were to receive PegIFNα-2a/RBV for a total treatment duration of 24 weeks (ie, 12 weeks of treatment with SMV + PegIFNα-2a/RBV, followed by 12 weeks of treatment with PegIFNα-2a/RBV).
- If the criterion above was not met: Subjects were to receive PegIFNα-2a/RBV for a total treatment duration of 48 weeks (ie, 12 weeks of treatment with SMV + PegIFNα-2a/RBV, followed by 36 weeks of treatment with PegIFNα-2a/RBV).

Subjects with prior viral relapse or breakthrough in the Phase 2/3 group who did not meet the criteria for treatment completion at 24 weeks, all prior nonresponder subjects in the Phase 2/3 group (null responders, partial responders and non-classifiable nonresponders), and subjects in the Phase 1 group were scheduled to continue treatment with PegIFNα-2a/RBV for a total of 48 weeks unless a virologic stopping rule was met.

Virologic stopping rules were incorporated to ensure that subjects in the Phase 2/3 and Phase 1 groups with no or extremely low chance of treatment success discontinued treatment in a timely manner in order to: 1) limit unnecessary exposure to SMV, PegIFNα-2a and RBV, and 2) limit the risk for evolution of resistant viral variants during continued therapy with SMV. According to the original virologic stopping rules, which applied to subjects enrolled prior to protocol amendment IV (OTDG group), subjects were to permanently discontinue all study medication when HCV RNA was >1,000 IU/mL at Week 4 or 12, or when HCV RNA was confirmed detectable at Week 24 or 36. The virologic stopping rules changed for subjects enrolled under protocol amendment IV or later amendments (MTDG group). Subjects in this group were to permanently discontinue all study medication when HCV RNA was ≥25 IU/mL at Week 4 or when HCV RNA was confirmed detectable at Week 12, 24, or 36. In the event virologic stopping rules were met at any given time point, all study medication was discontinued permanently. Virologic stopping rules overruled treatment continuation rules at all times.

For all subjects, there was a follow-up period of 24 weeks after the planned EOT (ie, Week 24 or Week 48). The total study duration (from screening until final study visit) for any given subject was maximum 78 weeks. The study was considered completed with the last visit of the last subject.

Number of Subjects (planned and analyzed): Five hundred thirty-nine HCV genotype 1 infected subjects were planned to be enrolled in the placebo group of previous Phase 2/3 SMV studies. It was estimated that 270 of these subjects would roll over into the C213 study, assuming that 50% of the subjects from the Phase 2/3 studies would fail treatment for virologic reasons and would roll over (based on the antiviral responses observed in the previous studies). The actual number of subjects rolling over and being treated in the C213 study was 125 (Phase 2/3 group). In addition to these 125 subjects, 16 HCV

genotype 1 infected subjects who had received short-term (up to 14 days) DAA treatment for HCV infection in the selected JRD-sponsored Phase 1 studies were treated in the C213 study (Phase 1 group). More disposition data are provided below.

	Simeprevir 150 mg 12 Wks PR 24/48		
	Phase 2/3 group	Phase 1 group	Total
Screened	142	17	159
Treated	125	16	141
Completed SMV	112 (89.6%)	15 (93.8%)	127 (90.1%)
Completed all study drugs[a]	98 (78.4%)	9 (56.3%)	107 (75.9%)
Study			
Completed	115 (92.0%)	12 (75.0%)	127 (90.1%)
Discontinued	10 (8.0%)	4 (25.0%)	14 (9.9%)

[a] It was noted after database lock that one of the subjects included in this category (a prior null responder in the Phase 2/3 group) did not complete all study therapy, but prematurely discontinued PegIFNα-2a/RBV treatment at Week 24 instead of Week 48 due to noncompliance with study treatment.

Diagnosis and Main Criteria for Inclusion:

Main inclusion criteria:

- Subject with HCV genotype 1 infection who was previously randomized to the placebo group of a Phase 2/3 SMV study and did not achieve undetectable HCV RNA levels at the EOT, or relapsed (confirmed detectable HCV RNA) within 1 year after EOT.

OR

- Subject with HCV genotype 1 infection who had received short-term (up to 14 days) DAA treatment for HCV infection in selected JRD-sponsored Phase 1 studies.

Subject had to have completed the last study-related assessment in the previous study.

Test Product, Dose and Mode of Administration, Batch Numbers:

- SMV (batch numbers: 364948, 4364948, 4365916, 4366524, 4367156): qd as 1 oral capsule of 150 mg.

Reference Therapy, Dose and Mode of Administration, Batch Numbers:

- PegIFNα-2a (Pegasys®) (batch numbers: 364923, 4364907, 4364922, 4364923, 4366221, 4366222, 4366223, 4366481, 4366525, 4366829, 4367429, 4367644): 180 µg once weekly, administered as weekly subcutaneous (SC) injections of 0.5 mL according to the manufacturers's prescribing information.
- RBV (Copegus®) (batch numbers: 364994, 364995, 4364994, 4364995, 4366521, 4366522, 4366520, 4366523, 4366991, 4367415):
  - If baseline body weight was <75 kg: total daily dose of 1,000 mg, administered as 400 mg (2 tablets of 200 mg) in the morning and 600 mg (3 tablets of 200 mg) in the evening, according to the manufacturer's prescribing information.
  - If baseline body weight was ≥75 kg: total daily dose of 1,200 mg, administered as 2 x 600 mg (3 tablets of 200 mg per intake, morning and evening), according to the manufacturer's prescribing information.

Criteria for Evaluation:

Efficacy Evaluations:

HCV RNA levels: Samples for the determination of HCV RNA were taken at predefined time points and processed in real-time.

Alanine aminotransferase (ALT) levels: ALT levels were determined as part of the biochemistry panel of the clinical laboratory tests. Samples for biochemistry were taken at predefined time points.

Resistance Determinations: Sequencing of the HCV NS3/4A region was performed to identify pre-existing polymorphisms and to characterize emerging HCV viral variants. The NS3/4A region was sequenced at baseline sample for all subjects and post-baseline for subjects not achieving SVR. The sequencing of the post-baseline samples was 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. Sequencing of the NS5B region was up to the Sponsor's discretion and was not performed.

Pharmacogenonomic and Exploratory Biomarker Analyses: If the *interleukin* (*IL) 28B* genotype status of the subject was not known at the start of the study, a mandatory pharmacogenomic blood sample for host *IL28B* genotyping had to be taken, preferably at baseline.

The study included the option for analyzing exploratory biomarkers at the RNA, protein and cellular level. The samples for these analyses were collected at predefined time points from all subjects who consented to participate in this study. The samples can be stored until biomarkers can be linked with treatment responses for meaningful evaluations.

An additional pharmacogenomic blood sample for exploratory host genotyping could be taken, preferably at baseline. This sample was optional and was only collected from subjects who consented separately to this pharmacogenomic component of the study (and where local regulations permitted).

Safety Evaluations: Safety and tolerability were evaluated throughout the study. These evaluations included monitoring of adverse events (AEs), clinical laboratory tests, vital signs, and physical examinations.

The safety monitoring and toxicity management plan in the protocol took into account AEs based on toxicities of the protease inhibitor class, clinical safety data of SMV, target organs identified in nonclinical studies, and toxicities reported with PegIFNα-2a and RBV.

Statistical Methods:

Sample Size Determination:

No formal sample size determination was done.

Populations in Analysis:

All analyses were done on the intent-to-treat (ITT) population (ie, all subjects who took at least 1 dose of investigational drug [SMV]). A per protocol analysis was planned to be performed on the primary endpoint (SVR12) if there were more than 10% of subjects with a major protocol deviation. The per protocol population consisted of all ITT subjects excluding those with a major protocol deviation.

Subject information, virology, and safety and tolerability were evaluated in the entire ITT population, as well as in the Phase 2/3 group and Phase 1 group separately.

Efficacy was also analyzed in the entire ITT population, as well as in the Phase 2/3 group and Phase 1 group separately. Within the Phase 2/3 group and within the Phase 1 group, efficacy was to be analyzed

separately in the two treatment duration guideline/virologic stopping rule subpopulations and also pooled. The 2 treatment duration guideline/virologic stopping rule subpopulations were:

- The OTDG group: subjects enrolled under the initial study protocol or protocol amendments I to III.
- The MTDG group: subjects enrolled under study protocol amendment IV or later.

Efficacy Analyses:

The primary efficacy parameter was the proportion of subjects with SVR12, defined as the proportion of subjects with undetectable HCV RNA (<25 IU/mL undetectable) at the actual EOT and HCV RNA <25 IU/mL detectable or undetectable 12 weeks after the planned EOT. Detectable HCV RNA after previous undetectability had to be confirmed by repeat HCV RNA testing within 3 weeks.

For the observed proportion of subjects with SVR12, a 95% confidence interval (CI) was constructed. Additionally, using a logistic regression model, the proportion of subjects with SVR12 and its corresponding 95% CI were provided, adjusted for baseline HCV RNA level, *IL28B* genotype (CC, CT, TT), and HCV genotype 1 subtype (1a/other, 1b). In addition, response to PegIFN/RBV treatment prior to this study (viral relapse, viral breakthrough, nonresponse) was included in the model for the Phase 2/3 group and whether a subject was treated with SMV during the previous study (SMV treatment-naïve, SMV treatment-experienced) was included in the model for the Phase 1 group.

Secondary efficacy parameters included the proportion of subjects:

- with SVR24.
- with undetectable HCV RNA (<25 IU/mL undetectable) and HCV RNA <25 IU/mL at all time points during treatment and follow-up, with focus on Week 4, Week 12, Week 24, Week 36, and Week 48.
- with on-treatment failure.
- with HCV RNA >1,000 IU/mL at Week 4.
- with viral breakthrough.
- with viral relapse.
- with normalized ALT levels at the EOT and at SVR time points.

For all response parameters, 95% CIs were constructed around the observed values. The same logistic regression model as applied for the primary efficacy parameter was applied for the analysis of other response parameters. The time to achieve undetectable HCV RNA was estimated using Kaplan-Meier plots. Descriptive statistics were calculated for the change in $\log_{10}$ HCV RNA levels from baseline at all time points.

Subgroup analyses were performed for the aforementioned parameters based on baseline HCV RNA levels, early viral response criteria, and other baseline characteristics including, but not limited to, race and age. In addition, a multivariate model was fitted on the SVR12 data exploring the combined effect of several factors. Subgroup analyses were also performed based on the *IL28B* genotype and response in the feeder study.

For the Phase 2/3 group, within-subject cross-tabulations were made of response pattern (viral relapse, viral breakthrough, null response, partial response, non-classifiable nonresponse) in the previous study and the present study.

Exploratory Biomarker Analyses:

At the time of report writing, no exploratory biomarker analyses had been performed.

Pharmacogenomics:

IL28B Genotyping: The baseline *IL28B* genotyping data were tabulated. Subgroup analyses were done to explore the effect of *IL28B* genotyping on the efficacy parameters by means of descriptive statistics and frequency tabulations.

Exploratory Host Genotyping: At the time of report writing, no exploratory host genotyping analyses had been performed.

Safety Analyses:

Adverse Events: The original terms reported in the electronic Case Report Forms by investigators to identify AEs were coded using the Medical Dictionary for Regulatory Activities. Type (system organ class and preferred term) and incidence of all AEs, as well as severity, drug relatedness, and outcome were tabulated. Special attention was given to subjects who had discontinued treatment for an AE, or who experienced a severe (at least grade 3) or serious adverse event (SAE).

Clinical Laboratory Tests: Data were summarized by type of laboratory test. Descriptive statistics (actual values and changes from baseline) were calculated for each laboratory parameter at each scheduled time point. Laboratory abnormalities were determined according to the World Health Organization grading table and in accordance with the normal ranges of the clinical laboratory.

Vital Signs: Descriptive statistics of pulse rate and blood pressure (systolic and diastolic) (supine) values and changes from baseline were summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits was summarized.

Physical Examination: Findings and changes from baseline were summarized at each scheduled time point. Abnormalities were listed.

RESULTS:

STUDY POPULATION:

Study and treatment completion/discontinuation data are presented in the table below.

	Simeprevir 150 mg 12 Wks PR 24/48		
	Phase 2/3 group	Phase 1 group	Total
Analysis set: intent-to-treat	125	16	141
Treatment duration of SMV (weeks)			
Median (range)	12.00 (4.6; 12.3)	12.10 (0.7; 12.1)	12.00 (0.7; 12.3)
Study completion/discontinuation			
Completed	115 (92.0%)	12 (75.0%)	127 (90.1%)
Discontinued	10 (8.0%)	4 (25.0%)	14 (9.9%)
Withdrawal by subject	5 (4.0%)	3 (18.8%)	8 (5.7%)
Lost to follow-up	5 (4.0%)	1 (6.3%)	6 (4.3%)
Treatment completion/discontinuation			
Completed all study therapy[a]	98 (78.4%)	9 (56.3%)	107 (75.9%)
Completed PR[a,b]	99 (79.2%)	9 (56.3%)	108 (76.6%)
Completed SMV	112 (89.6%)	15 (93.8%)	127 (90.1%)
Discontinued SMV	13 (10.4%)	1 (6.3%)	14 (9.9%)
Adverse event[c]	3 (2.4%)	0	3 (2.1%)
Withdrawal by subject	2 (1.6%)	1 (6.3%)	3 (2.1%)
Subject reached a virologic endpoint[d]	8 (6.4%)	0	8 (5.7%)

[a] It was noted after database lock that one of the subjects included in these categories (a prior null responder in the Phase 2/3 group) did not complete all study therapy, but prematurely discontinued PegIFNα-2a/RBV treatment at Week 24 instead of Week 48 due to noncompliance with study treatment.
[b] Subjects who completed at least one study drug (RBV or PegIFNα-2a) at Week 24 (for subjects previously enrolled in an SMV Phase 2 or 3 study and who met the RGT criteria) or at Week 48 (all other subjects).
[c] May include subjects who stopped SMV because they had to stop RBV and/or PegIFNα-2a due to an adverse event.
[d] Subject met a virologic stopping rule.

Information presented in the table is based upon "administration of SMV", "Treatment Termination" (investigator's evaluation), and "Trial Termination" (investigator's evaluation) electronic case report form pages.

More than half of the subjects were male (64.0% [80/125] in the Phase 2/3 group and 81.3% [13/16] in the Phase 1 group). The majority of subjects were white (96.8% [121/125] in the Phase 2/3 group and 87.5% [14/16] in the Phase 1 group). The median age was 51.0 years (range: 22-72) in the Phase 2/3 group and 52.5 years (range: 33-65) in the Phase 1 group. The median body mass index was 27.40 kg/m^2 (range: 18.9-45.8) in the Phase 2/3 group and 27.05 kg/m^2 (range: 20.4-35.3) in the Phase 1 group. In the Phase 2/3 group, 16.0% of subjects (20/125) had the *IL28B* CC genotype, 69.6% (87/125) the *IL28B* CT genotype, and 14.4% (18/125) the *IL28B* TT genotype. In the Phase 1 group, these *IL28B* genotypes were observed in 6.3% (1/16), 56.3% (9/16), and 37.5% of subjects (6/16), respectively. In the Phase 2/3 group, 38.3% of subjects (46/120) had homeostatic model assessment of insulin resistance (HOMA-IR) <2, 35.8% (43/120) had HOMA-IR between 2 and 4, and 25.8% (31/120) had HOMA-IR >4. In the Phase 1 group, HOMA-IR <2, between 2 and 4, and >4 were observed in 28.6% (4/14), 50.0% (7/14), and 21.4% of subjects (3/14), respectively.

The median HCV RNA level at baseline was 6.53 log_{10} IU/mL (range: 4.9-7.8) in the Phase 2/3 group and 6.68 log_{10} IU/mL (range: 5.6-7.2) in the Phase 1 group. High baseline plasma HCV RNA levels, defined as plasma HCV RNA >800,000 IU/mL, were observed in the majority of subjects (86.4% [108/125] in the Phase 2/3 group and 93.8% [15/16] in the Phase 1 group).

All subjects were infected with HCV genotype 1. In the Phase 2/3 subjects, HCV genotype 1a and 1b were observed in 40.0% (50/125) and 60.0% (75/125), respectively, while in the Phase 1 group these genotype subtypes were observed in 87.5% (14/16) and 12.5% (2/16), respectively. A Q80K polymorphism was observed in 24.0% (12/50) and 21.4% (3/14) of HCV genotype 1a subjects in the Phase 2/3 group and Phase 1 group, respectively. None of the HCV genotype 1b infected subjects had a Q80K polymorphism.

At baseline, 68.0% of subjects (85/125) in the Phase 2/3 group and 81.3% of subjects (13/16) in the Phase 1 group had METAVIR F0 to F2, 14.4% (18/125) and 18.8% (3/16), respectively, had F3, and 17.6% (22/125) and 0% (0/16), respectively, had F4.

Subjects in the Phase 2/3 group had rolled over from the following studies: C205 (6.4%; 8/125), C206 (22.4%, 28/125), C208 (20.0%; 25/125), C216 (22.4%; 28/125), and HPC3007 (28.8%; 36/125). During these studies, the subjects had not achieved SVR, but had relapse (44.0%; 55/125), viral breakthrough (8.0%; 10/125), null response (24.0%; 30/125), partial response (22.4%; 28/125), or were non-classifiable nonresponders (1.6%; 2/125).

Of the 16 subjects in the Phase 1 group, 8 subjects (50.0%) had previously received 150 mg SMV every 24 hours and 1,000 mg of TMC647055, a non-nucleoside NS5B polymerase inhibitor, every 12 hours for 10 days in study TMC647055HPC1001. The remaining 8 subjects (50.0%) either had received placebo or 1,000 mg of TMC649128, a nucleoside NS5B polymerase inhibitor, every 24 hours for 10 days or placebo or 1,600 mg TMC649128 every 12 hours for 14 days in study TMC649128HPC1002. Consequently, half of the subjects in the Phase 1 group were SMV treatment-experienced and half were SMV treatment-naïve.

	Simeprevir 150 mg 12 Wks PR 24/48		
	Phase 2/3 group	Phase 1 group	Total
Analysis Set: intent-to-treat	125	16	141
Demographic characteristics			
Gender			
N	125	16	141
Female	45 (36.0%)	3 (18.8%)	48 (34.0%)
Male	80 (64.0%)	13 (81.3%)	93 (66.0%)
Race			
N	125	16	141
White	121 (96.8%)	14 (87.5%)	135 (95.7%)
Black or African American	3 (2.4%)	1 (6.3%)	4 (2.8%)
American Indian or Alaska Native	0	1 (6.3%)	1 (0.7%)
Native Hawaiian or Other Pacific Islander	1 (0.8%)	0	1 (0.7%)
Asian	0	0	0
Multiple	0	0	0
Region			
N	125	16	141
Asia-Pacific	9 (7.2%)	0	9 (6.4%)
Europe	87 (69.6%)	16 (100.0%)	103 (73.0%)
North-America	24 (19.2%)	0	24 (17.0%)
South-America	5 (4.0%)	0	5 (3.5%)
Age (years)			
N	125	16	141
Mean (SD)	50.0 (10.44)	51.8 (8.91)	50.2 (10.27)
Median	51.0	52.5	52.0
Range	(22; 72)	(33; 65)	(22; 72)
Body Mass Index (kg/m^2)			
N	125	16	141
Mean (SD)	27.60 (4.829)	28.13 (4.068)	27.66 (4.739)
Median	27.40	27.05	27.20
Range	(18.9; 45.8)	(20.4; 35.3)	(18.9; 45.8)

	Simeprevir 150 mg 12 Wks PR 24/48		
	Phase 2/3 group	Phase 1 group	Total
IL28B Genotype			
N	125	16	141
CC	20 (16.0%)	1 (6.3%)	21 (14.9%)
CT	87 (69.6%)	9 (56.3%)	96 (68.1%)
TT	18 (14.4%)	6 (37.5%)	24 (17.0%)
HOMA-IR			
N	120	14	134
<2	46 (38.3%)	4 (28.6%)	50 (37.3%)
≥2 - ≤4	43 (35.8%)	7 (50.0%)	50 (37.3%)
>4	31 (25.8%)	3 (21.4%)	34 (25.4%)
Baseline disease characteristics			
Response to the last course of PegIFN/RBV therapy in Phase 2/3 study			
N	125	-	125
Viral relapser	55 (44.0%)	-	55 (44.0%)
Viral breakthrough	10 (8.0%)	-	10 (8.0%)
Nonresponder	60 (48.0%)	-	60 (48.0%)
Partial responder	28 (22.4%)	-	28 (22.4%)
Null responder	30 (24.0%)	-	30 (24.0%)
Other[a]	2 (1.6%)	-	2 (1.6%)
Treatment history in Phase 1 group			
N	-	16	16
SMV treatment-naïve	-	8 (50.0%)	8 (50.0%)
SMV treatment-experienced	-	8 (50.0%)	8 (50.0%)
Baseline HCV RNA level (log_{10} IU/mL)			
N	125	16	141
Mean (SD)	6.48 (0.550)	6.62 (0.384)	6.50 (0.534)
Median	6.53	6.68	6.54
Range	(4.9; 7.8)	(5.6; 7.2)	(4.9; 7.8)
Baseline HCV RNA category (IU/mL)			
N	125	16	141
<400000	12 (9.6%)	0	12 (8.5%)
≥400000 - ≤800000	5 (4.0%)	1 (6.3%)	6 (4.3%)
>800000	108 (86.4%)	15 (93.8%)	123 (87.2%)
METAVIR fibrosis score[b]			
N	125	16	141
Score F0-F1	49 (39.2%)	7 (43.8%)	56 (39.7%)
Score F2	36 (28.8%)	6 (37.5%)	42 (29.8%)
Score F3	18 (14.4%)	3 (18.8%)	21 (14.9%)
Score F4	22 (17.6%)	0	22 (15.6%)
HCV geno/subtype[c] and baseline Q80K polymorphism			
N	125	16	141
1a	50 (40.0%)	14 (87.5%)	64 (45.4%)
With Q80K	12 (24.0%)	3 (21.4%)	15 (23.4%)
Without Q80K	38 (76.0%)	11 (78.6%)	49 (76.6%)
1b	75 (60.0%)	2 (12.5%)	77 (54.6%)

[a] Nonresponder, but not classifiable.
[b] Limited to results from METAVIR scoring system.
[c] HCV GENO/SUBTYPE (Coalesce) is based on the NS5B assay, and if not available on LIPA HCV II or Trugene results.
Subjects were rolled over from the following SMV Phase 2/3 studies: TMC435-TiDP16-C205, TMC435-TiDP16-C206, TMC435-TiDP16-C208, TMC435-TiDP16-C216, TMC435HPC3007, and Phase 1 studies: TMC647055HPC1001 and TMC649128HPC1002.

Overall, major protocol deviations were observed for 15 subjects (10.6%): 14 subjects (11.2%) in the Phase 2/3 group and 1 subject (6.3%) in the Phase 1 group. Since the percentage of subjects with a major

protocol deviation (overall and in the Phase 2/3 group) was >10%, a per protocol analysis was performed on the primary efficacy endpoint.

	Simeprevir 150 mg 12 Wks PR 24/48		
	Phase 2/3 group	Phase 1 group	Total
Analysis set: intent-to-treat	125	16	141
Subjects with major deviation	14 (11.2%)	1 (6.3%)	15 (10.6%)
Developed withdrawal criteria but not withdrawn	2 (1.6%)	0	2 (1.4%)
Entered but did not satisfy criteria	9 (7.2%)	0	9 (6.4%)
Received wrong treatment or incorrect dose	1 (0.8%)	0	1 (0.7%)
Other	4 (3.2%)	1 (6.3%)	5 (3.5%)

EFFICACY RESULTS:

Primary Efficacy Endpoint

In the ITT population of the Phase 2/3 group, the SVR12 rate was 69.6% (87/125) with 95% CI (61.5%, 77.7%). In the per protocol population, the SVR12 rate was 73.0% (81/111) with 95% CI (64.7%, 81.2%).

Within the Phase 2/3 group, the OTDG group consisted of 98 subjects and the MTDG group of 27 subjects. Similar SVR12 rates were observed in the OTDG (69.4% [68/98]) and MTDG group (70.4% [19/27]).

The SVR12 rate in subjects in the Phase 2/3 group with HCV genotype 1a (66.0% [33/50]) was similar to the SVR12 rate in subjects with HCV genotype 1b (72.0% [54/75]). Subjects with HCV genotype 1a with versus without a baseline Q80K polymorphism had SVR12 rates of 66.7% (8/12) and 65.8% (25/38), respectively. By response to prior PegIFN/RBV treatment, the SVR12 rate was the highest in prior relapsers (92.7% [51/55]). SVR12 rates were 60.0% (6/10) in subjects with prior viral breakthrough, 64.3% (18/28) in prior partial responders, 36.7% (11/30) in prior null responders, and 50.0% (1/2) in non-classifiable prior nonresponders. The SVR12 rate was higher in subjects with *IL28B* genotype CC (85.0% [17/20]) as compared to CT (66.7% [58/87]) and TT (66.7% [12/18]). The SVR12 rate was also higher in subjects with METAVIR F0-F2 (75.3% [64/85]) as compared to F3 (61.1% [11/18]) and F4 (54.5% [12/22]). Finally, the SVR12 rate was higher in subjects with HOMA-IR <2 (84.8% [39/46]) as compared to HOMA-IR between 2 and 4 (58.1% [25/43]) or >4 (64.5% [20/31]).

In the ITT population of the Phase 1 group, 6 of the 16 subjects (37.5%) achieved SVR12 (95% CI: [13.8%, 61.2%]). All 16 subjects from the Phase 1 group were enrolled prior to protocol amendment IV and were categorized under the OTDG group. The original virologic stopping rules applied to all Phase 1 group subjects. No RGT duration guidelines applied to them.

Of the 16 subjects in the Phase 1 group, 14 subjects were infected with HCV genotype 1a and 3 of those subjects (all 3 without prior exposure to SMV) had a Q80K polymorphism at baseline. Two of the 3 HCV genotype 1a infected subjects with Q80K at baseline achieved SVR12. Among the 8 subjects with prior exposure to SMV, 6 subjects had emerging mutations, all R155K, during the short-term exposure to SMV in the Phase 1 study. At baseline of study C213, R155K was still detected in 2 of those subjects. Three of the 8 subjects with prior exposure to SMV achieved SVR12, including 1 of the 2 subjects with R155K at baseline.

	Observed		Model Adjusted[a]
	n/N (%)	95% CI[c]	% (95% CI)[b]
Analysis set: intent-to-treat			
SVR12			
Simeprevir 150 mg 12 Wks PR24/48			
All subjects	93/141 (66.0)	58.1;73.8	64.4 (48.7;80.0)
Phase 2/3 group	87/125 (69.6)	61.5;77.7	74.9 (64.3;85.4)
Viral relapser[d]	51/55 (92.7)	85.9;99.6	
Viral breakthrough[d]	6/10 (60.0)	29.6;90.4	
Nonresponder[d,e]	30/60 (50.0)	37.3;62.7	
Partial responder[d]	18/28 (64.3)	46.5;82.0	
Null responder[d]	11/30 (36.7)	19.4;53.9	
Other[d,f]	1/2 (50.0)	0.0;100.0	
Phase 1 group	6/16 (37.5)	13.8;61.2	52.3 (23.6;81.0)
SMV naïve	3/8 (37.5)	4.0;71.0	
SMV experienced	3/8 (37.5)	4.0;71.0	

[a] Using logistic regression the proportion is adjusted for baseline HCV RNA level, IL28B genotype (CC, CT, TT), HCV geno/subtype (based on NS5B assay, and if not available LIPA HCV II or Trugene result is used) categorized as 1b versus any other geno/subtype), and Treatment Phase group (Phase 1 group, Phase 2/3 group).
[b] 95% CI based on the delta method and normal approximation.
[c] 95% CI based on the normal approximation.
[d] Prior response to PegIFN and RBV treatment.
[e] Combination of Partial responder, Null responder and Other.
[f] Nonresponder, but not classifiable.

Secondary Efficacy Endpoints

All subjects with SVR12 in the Phase 2/3 and Phase 1 groups achieved SVR24.

The majority of subjects eligible for RGT (ie, subjects with prior viral relapse or breakthrough in the Phase 2/3 group) met the RGT criteria: 89.2% (58/65) of the eligible subjects from the MTDG group and the OTDG group to whom the modified RGT criteria were applied retrospectively. The SVR12 rate in this group of subjects was 89.7% (52/58).

Rapid virologic response (RVR) was achieved in 72.0% of subjects on treatment (90/125) in the Phase 2/3 group and in 46.7% of subjects on treatment (7/15) in the Phase 1 group. The SVR12 rate in subjects with RVR was 81.1% (73/90) in the Phase 2/3 group and 42.9% (3/7) in the Phase 1 group.

The proportion of subjects with on-treatment failure was 16.0% (20/125) in the Phase 2/3 group and 18.8% (3/16) in the Phase 1 group.

Viral breakthrough was observed in 9.6% of subjects (12/125) in the Phase 2/3 group and 6.7% of subjects (1/15) in the Phase 1 group. Ten of the 12 subjects with viral breakthrough in the Phase 2/3 group had been null responders to PegIFN/RBV treatment in the feeder study.

Post-treatment failure was observed in 14.4% of subjects (18/125) in the Phase 2/3 group and 43.8% of subjects (7/16) in the Phase 1 group. Most subjects with post-treatment failure had viral relapse: 12.0% (15/125) in the Phase 2/3 group and 31.3% (5/16) in the Phase 1 group. Missing data at the SVR12 assessment time point was the reason for post-treatment failure in 2.4% of subjects (3/125) in the Phase 2/3 group and 12.5% of subjects (2/16) in the Phase 1 group.

Of the subjects with undetectable HCV RNA at end of treatment, 15 of the 104 subjects in the Phase 2/3 group (14.4%) and 5 of the 12 subjects in the Phase 1 group (41.7%) had viral relapse. Viral relapse occurred within the first 12 weeks after the end of treatment in all cases. By response to prior PegIFN/RBV treatment, it was observed in the Phase 2/3 group that 5 of the 16 prior null responders

(31.3%), 5 of the 24 prior partial responders (20.8%), 1 of the 8 subjects with prior viral breakthrough (12.5%), and 4 of the 55 prior relapsers (7.3%) had viral relapse.

Twenty-seven of the 33 subjects (81.8%) in the Phase 2/3 group and 7 of the 8 subjects (87.5%) in the Phase 1 group with failure and sequencing data available had emerging mutations at the time of failure. All these subjects had mutations at NS3 amino acid positions 80, 122, 155, and/or 168.

SAFETY RESULTS:

Adverse Events

During the SMV + PegIFNα-2a/RBV treatment phase, the most frequent AEs (by preferred term) (in >20% of subjects) were fatigue (32.6%), neutropenia (22.7%), and influenza-like illness (22.0%). These AEs are known side effects of treatment with PegIFNα-2a/RBV.

During the SMV + PegIFNα-2a/RBV treatment phase, the majority of AEs were grade 1 or 2 in severity. Grade 3 or 4 AEs were reported in 29.1% of subjects and grade 3 or 4 AEs considered at least possibly related to SMV by the investigator were reported in 6.4% of subjects. The most frequent grade 3 or 4 AE (in >5% of subjects) was neutropenia (14.2%).

The proportion of subjects who experienced at least 1 AE that was considered at least possibly related to SMV by the investigator was 66.0%.

The incidence of AEs leading to permanent discontinuation of study drugs was low. Three subjects (2.1%) permanently discontinued SMV treatment due to an AE (1 subject due to hyperbilirubinemia, 1 subject due to a panic attack, and 1 subject due to a photosensitivity reaction). The last 2 AEs also led to permanent discontinuation of RBV and PegIFNα-2a.

There were no deaths and the incidence of SAEs was low. During the SMV + PegIFNα-2a/RBV treatment phase, SAEs occurred in 5 subjects (3.5%). The reported SAEs were grade 2 gastritis, grade 2 bronchitis, grade 3 pancytopenia, grade 3 hand fracture, and grade 3 renal cell carcinoma. None of the SAEs were considered at least possibly related to SMV, PegIFNα-2a, or RBV, except for pancytopenia, which was considered very likely related to RBV and possibly related to PegIFNα-2a.

	Simeprevir+PR Phase	Entire Treatment Phase
	Simeprevir 150 mg 12 Wks PR 24/48	Simeprevir 150 mg 12 Wks PR 24/48
Analysis set: intent-to-treat	141	141
Any AE	128 (90.8%)	131 (92.9%)
Worst grade 1 or 2 AE	87 (61.7%)	81 (57.4%)
Worst grade 1	45 (31.9%)	37 (26.2%)
Worst grade 2	42 (29.8%)	44 (31.2%)
Worst grade 3 or 4 AE	41 (29.1%)	50 (35.5%)
Worst grade 3	36 (25.5%)	45 (31.9%)
Worst grade 4	5 (3.5%)	5 (3.5%)
At least possibly related to SMV	9 (6.4%)	9 (6.4%)
Treatment-related AE	127 (90.1%)	131 (92.9%)
At least possibly related to SMV	93 (66.0%)	93 (66.0%)
At least possibly related to RBV	99 (70.2%)	109 (77.3%)
At least possibly related to PegIFNα-2a	123 (87.2%)	126 (89.4%)
Any AE with fatal outcome	0	0
Any SAE	5 (3.5%)	9 (6.4%)
At least possibly related to SMV	0	0
AE leading to permanent stop[a]	6 (4.3%)	9 (6.4%)
SMV[b]	3 (2.1%)	3 (2.1%)
SMV only	1 (0.7%)	1 (0.7%)
SMV and PegIFNα-2a	0	0
SMV and RBV	0	0
SMV, PegIFNα-2a and RBV	2 (1.4%)	2 (1.4%)
PegIFNα-2a and/or RBV	3 (2.1%)	6 (4.3%)
PegIFNα-2a only	0	0
RBV only	0	0
PegIFNα-2a and RBV	3 (2.1%)	6 (4.3%)

[a] Permanent stop of at least one drug.
[b] Without regard to PegIFNα-2a and RBV.
Allocation of an AE that led to permanent stop of study drug(s) to a treatment phase is based on the onset date of the AE.

Some AEs were considered of special or clinical interest and grouped accordingly. Increased bilirubin was considered an AE of special interest and rash (any type), pruritus, anemia, photosensitivity conditions, neutropenia, and dyspnea were considered AEs of clinical interest. There were no unexpected observations with regard to the frequency or severity of the reported events of special/clinical interest.

The majority of the AEs of special/clinical interest were grade 1 or 2 in severity. During the SMV + PegIFNα-2a/RBV treatment phase, grade 4 neutropenia AEs were reported in 3.5% of subjects and grade 3 neutropenia AEs in 11.3% of subjects. There were no other grade 4 AEs of special/clinical interest than neutropenia AEs, but other grade 3 AEs of special/clinical interest were reported in ≤3.5% of subjects during the SMV + PegIFNα-2a/RBV treatment phase.

None of the AEs of special/clinical interest were serious and AEs of special/clinical interest leading to permanent discontinuation of study drugs were rare. During the SMV + PegIFNα-2a/RBV treatment phase, grade 3 hyperbilirubinemia (an increased bilirubin AE) led to permanent discontinuation of SMV in 1 subject (0.7%) and a grade 3 photosensitivity reaction (a rash AE, which was also a photosensitivity condition) led to permanent discontinuation of SMV, PegIFNα-2a, and RBV in 1 subject (0.7%) (as mentioned above).

	Simeprevir+PR Phase	Entire Treatment Phase
	Simeprevir 150 mg 12 Wks PR 24/48	Simeprevir 150 mg 12 Wks PR 24/48
Analysis set: intent-to-treat	141	141
Events of special interest	17 (12.1%)	17 (12.1%)
Increased bilirubin	17 (12.1%)	17 (12.1%)
Events of clinical interest	78 (55.3%)	87 (61.7%)
Rash (any type)	31 (22.0%)	36 (25.5%)
Pruritus	25 (17.7%)	26 (18.4%)
Photosensitivity conditions	8 (5.7%)	8 (5.7%)
Neutropenia	33 (23.4%)	38 (27.0%)
Anemia	11 (7.8%)	23 (16.3%)
Dyspnea	15 (10.6%)	17 (12.1%)

Subjects are counted only once for any given event, regardless of the number of times they actually reported the same event.
Adverse events are coded using MedDRA version 14.1.
Increased bilirubin includes MedDRA preferred terms: "Bilirubin conjugated abnormal", "Bilirubin conjugated increased", "Bilirubin excretion disorder", "Bilirubinuria", "Blood bilirubin abnormal", "Blood bilirubin increased", "Blood bilirubin unconjugated increased", "Hyperbilirubinaemia", "Icterus index increased", "Jaundice", "Jaundice cholestatic", "Jaundice extrahepatic obstructive", "Jaundice hepatocellular", "Ocular Icterus","Urine bilirubin increased", "Yellow skin".
Rash (Any Type) includes MedDRA HLTs: "Erythemas", "Papulosquamous conditions", "Rashes, eruptions and exanthems NEC", "Photosensitivity conditions", MedDRA preferred term "Sunburn", MedDRA SMQ "Severe cutaneous adverse reaction": narrow scope) and selected terms of the broad scope.
Pruritus includes MedDRA HLT "Pruritus NEC".
Photosensitivity conditions includes MedDRA HLT "Photosensitivity conditions" and MedDRA preferred term "Sunburn".
Neutropenia includes MedDRA preferred terms "Neutropenia", "Neutrophil count decreased".
Anemia includes MedDRA preferred terms "Anaemia", "Haemoglobin decreased", "Haemolytic anemia".
Dyspnea includes MedDRA preferred terms "Acute respiratory distress syndrome", "Cardiorespiratory arrest", "Dyspnea", "Dyspnea exertional", "Dyspnea at rest", "Dyspnea at rest", "Dyspnea paroxysmal nocturnal", "Hyperventilation", "Nocturnal dyspnea", "Orthopnea", "Respiratory arrest", "Respiratory distress", "Tachypnea".

Overall, observations made during the entire treatment phase were in line with the SMV + PegIFNα-2a/RBV treatment phase.

Clinical Laboratory Evaluation

Among the laboratory parameters for which treatment-emergent abnormalities with worst grade ≥3 were noted, the most frequent treatment-emergent abnormalities (in >25% of subjects) during the SMV + PegIFNα-2a/RBV treatment phase were decreases in neutrophil and precursor count (79.3%, any grade), hyperbilirubinemia (53.6%, any grade), and decreases in platelet count (25.7%, any grade).

Decrease in neutrophil and precursor count was the only graded treatment-emergent laboratory abnormality for which grade 3 or 4 abnormalities were observed in >10% of subjects (19.3%).

Vital Signs

During the SMV + PegIFNα-2a/RBV treatment phase, the most frequent treatment-emergent abnormalities in vital signs (in >5% of subjects) were increases in supine systolic blood pressure (9.3%) and supine diastolic blood pressure (8.6%). All abnormalities were at most grade 2 in severity. Adverse events related to vital signs were infrequent.

STUDY LIMITATIONS:

The low sample size in the Phase 1 group was considered a study limitation by the sponsor.

CONCLUSION(S):

In HCV genotype 1 infected subjects who previously participated in the placebo group of a Phase 2/3 SMV study, SVR12 rates of 69.6% (87/125) were achieved after treatment with SMV 150 mg qd for 12 weeks in combination with PegIFNα-2a and RBV for 24 or 48 weeks. The SVR12 rate was the highest in prior relapsers (92.7%) and SVR12 rates of 60.0% (6/10), 64.3% (18/28), and 36.7% (11/30) were observed in subjects with prior viral breakthrough, prior partial response, and prior null response, respectively. Similar SVR12 rates were observed in subjects with HCV genotype 1a (66.0% [33/50]) and HCV genotype 1b (72.0% [54/75]). Among subjects with HCV genotype 1a, SVR12 rates were similar in subjects with (66.7% [8/12]) versus without (65.8% [25/38]) a baseline Q80K polymorphism. The majority of subjects eligible for RGT (ie, subjects with prior viral relapse or breakthrough) met the RGT criteria. The SVR12 rate in this group of subjects was 89.7% (52/58). On-treatment failure was observed in 16.0% of subjects (20/125) and post-treatment failure (mainly relapse) in 14.4% of subjects (18/125).

Of the 16 HCV genotype 1 infected subjects who previously received short-term DAA treatment for HCV infection in the selected JRD-sponsored Phase 1 studies, 6 (37.5%) achieved SVR12 after treatment with SMV 150 mg qd for 12 weeks in combination with PegIFNα-2a and RBV for 48 weeks.

There were no unexpected safety findings and no fatal events reported. Three subjects (2.1%) permanently discontinued SMV treatment due to an AE (1 subject due to hyperbilirubinemia, 1 subject due to a panic attack, and 1 subject due to a photosensitivity reaction).

Janssen Research & Development *

Erratum 1 to Clinical Study Report dated 27 November 2015

A Phase 3, Open-label Trial of TMC435 in Combination With Peginterferon α-2a and Ribavirin for HCV Genotype 1 Infected Subjects who Participated in the Placebo Group of a Phase 2/3 TMC435 Study (C201, C205, C206, C208, C216 or HPC3007), or who Received Short-term (up to 14 Days) Direct-acting Antiviral Treatment for Hepatitis C Infection in a Selected Tibotec**-sponsored Phase 1 Study

TMC435-TiDP16-C213

Protocol TMC435-TiDP16-C213; Phase 3

TMC435 (simeprevir)

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Status:	Approved
Date:	2 March 2016
Prepared by:	Janssen Research & Development, a division of Janssen Pharmaceutica NV
EDMS number:	EDMS-ERI-119717171, 1.0

GCP Compliance: This study was conducted in compliance with Good Clinical Practice, including the archival of essential documents.

1. SUMMARY OF CHANGES

The following items were found in the clinical study report after the final approval. Overall, the conclusions as stated in the CSR remain valid after correction of these errata.

Bold and underlined is used to indicate addition of text; ~~strikethrough~~ is used to indicate deletion of text.

Page	Section	Description of Errata
10	Synopsis	**Study Center(s):** Subjects were screened and treated at 75 sites in 22 countries: Australia (4 sites), New Zealand (2 sites), Austria (2 sites), Belgium (4 sites), Bulgaria (1 site), Germany (7 sites), Spain (3 sites), France (4 sites), United Kingdom (2 sites), ~~Iceland~~ **Israel** (2 sites), Italy (1 site), The Netherlands (2 sites), Poland (5 sites), Portugal (3 sites), Romania (1 site), Russian Federation (8 sites), Ukraine (3 sites), Canada (3 sites), Mexico (1 site), United States (14 sites), Argentina (2 sites), Brazil (1 site).
83-84	Section 4.1	Iceland was replaced by Israel in Attachment TSIDS02 and Attachment LSIDS02. Update of Table 9 (see below).

Table 9: Subjects by Region and Country; ITT

	Simeprevir 150 mg 12 Wks PR 24/48		
	Phase II/III group	Phase I group	Total
Analysis Set: Intent-to-treat	125	16	141
Asia-pacific	9 (7.2%)	0	9 (6.4%)
Australia	7 (5.6%)	0	7 (5.0%)
New Zealand	2 (1.6%)	0	2 (1.4%)
Europe	87 (69.6%)	16 (100.0%)	103 (73.0%)
Austria	6 (4.8%)	0	6 (4.3%)
Belgium	3 (2.4%)	6 (37.5%)	9 (6.4%)
Bulgaria	1 (0.8%)	0	1 (0.7%)
France	6 (4.8%)	0	6 (4.3%)
Germany	13 (10.4%)	0	13 (9.2%)
~~Iceland~~ **Israel**	3 (2.4%)	0	3 (2.1%)
Italy	1 (0.8%)	0	1 (0.7%)
Netherlands	0	10 (62.5%)	10 (7.1%)
Poland	18 (14.4%)	0	18 (12.8%)
Portugal	4 (3.2%)	0	4 (2.8%)
Romania	2 (1.6%)	0	2 (1.4%)
Russian Federation	16 (12.8%)	0	16 (11.3%)
Spain	7 (5.6%)	0	7 (5.0%)
Ukraine	5 (4.0%)	0	5 (3.5%)
United Kingdom	2 (1.6%)	0	2 (1.4%)
North-America	24 (19.2%)	0	24 (17.0%)
Canada	3 (2.4%)	0	3 (2.1%)
Mexico	1 (0.8%)	0	1 (0.7%)
United States	20 (16.0%)	0	20 (14.2%)
South-America	5 (4.0%)	0	5 (3.5%)
Argentina	2 (1.6%)	0	2 (1.4%)
Brazil	3 (2.4%)	0	3 (2.1%)

~~[TSIDS02A.rtf] [TMC435\C213\DBR_FINAL_ANALYSIS\RE_FINAL_ANALYSIS\tsids02a.sas] 17JUL2015, 09:08~~

[TSIDS02A.rtf] [TMC435\C213\DBR_FINAL_ANALYSIS\RE_FINAL_ANALYSIS\tsids02a.sas] 18FEB2016, 16:56

SIGNATURE OF SPONSOR'S RESPONSIBLE MEDICAL OFFICER

NAME:	Wolfgang Jessner
TITLE:	MD
SIGNATURE:	eSignature has been applied on the next page.
DATE:	

SIGNATURES

Signed by	Date	Justification
Wolfgang Jessner	02Mar2016, 10:25:18 AM, UTC	Document Approval

Protocol ID	Region	Investigational site
TMC435-TIDP16-C213	Argentina	Cidea Paraguay C2 SS Buenos Aires 2035 Argentina
TMC435-TIDP16-C213	Argentina	Hospital Centenario Justo José de Urquiza 3101 Rosario, Santa Fe 2000 Argentina
TMC435-TIDP16-C213	Australia	Alfred Hospital, Commercial road, Melbourne, VIC 3004 Australia
TMC435-TIDP16-C213	Australia	Westmead Hospital Centre for Infectious Diseases Icpmr Darcy Rd, Sydney 2145 Australia
TMC435-TIDP16-C213	Australia	Princess Alexandra Hospital Ipswich Road, Woolloongabba, Queensland 4102 Australia
TMC435-TIDP16-C213	Australia	Westmead Hospital Centre for Infectious Diseases Hospital Road, Concord,Nsw 2139 Australia
TMC435-TIDP16-C213	Austria	Allgemeines Krankenhaus der Stadt Wien Währinger Gürtel 18-20 Wien 1090 Austria
TMC435-TIDP16-C213	Austria	Wilhelminenspital der Stadt Wien Montleartstrasse 37 Vienna 1160 Austria
TMC435-TIDP16-C213	Belgium	Cliniques Universitaires Saint-Luc Avenue Hippocrate 10 Ucl 10/2155 Bruxelles 1200 Belgium
TMC435-TIDP16-C213	Belgium	Universitair Ziekenhuis Gent De Pintelaan 185 Gent 9000 Belgium
TMC435-TIDP16-C213	Belgium	Hopital Erasme Route De Lennik 808

		Bruxelles 1070 Belgium
TMC435-TIDP16-C213	Belgium	Zna Stuivenberg Lange Beeldekensstraat 267 Antwerpen 2060 Belgium
TMC435-TIDP16-C213	Brazil	Centro De Referência e Treinamento Dst/Aids R Sta Cruz 81 Sao Paulo 02141-000 Brazil
TMC435-TIDP16-C213	Bulgaria	University Multiprofile Hospital for Active Treatment "Alexandrovska" 1 Georgi Sofiiski Str Sofia 1431 Bulgaria
TMC435-TIDP16-C213	Canada	Toronto General Hospital Ncsb11C-1252, 585 University Avenue Toronto M5G 2N2 Canada
TMC435-TIDP16-C213	Canada	Montreal Chest Institute Researchetics Board Of Muhc 3650 Urbain St Montreal H3A 1A1 Canada
TMC435-TIDP16-C213	Canada	Toronto Western Hosptial Health Network University Toronto,ON M5T 2S8 Canada
TMC435-TIDP16-C213	France	Chu de Nice, Hopital de l'Archet 151 Rte Saint Antoine De Ginestiere Nice Cedex 06202 France
TMC435-TIDP16-C213	France	Centre Hospitalier Universitaire BP 217X Grenoble 38043 France
TMC435-TIDP16-C213	France	Hopital saint antoine 184, rue du Faubourg Saint-Antoine Paris 75571 France
TMC435-TIDP16-C213	France	Hopital De La Croix rousse 103 Grande rue De La Croix rousse Lyon 69004 France

TMC435-TIDP16-C213	Germany	Keikawus Arasteh Epimed GmbH Rubensstrasse 125 Berlin 12157 Germany
TMC435-TIDP16-C213	Germany	Hartwig Klinker universitätsklinikum würzburg Abteilung Dür Neuroradiologies - Josef Schneider S Würzburg 97080 Germany
TMC435-TIDP16-C213	Germany	Holger Hinrichsen Leberstudienzentrum Kiel GbR Preetzer Chaussee 134 Kiel 24146 Germany
TMC435-TIDP16-C213	Germany	Stefan Zeuzem Klinikum der Johann-Wolfgang-Goethe Universität - Med. Klinik I Theodor-Stern-Kai 7 Frankfurt 60590 Germany
TMC435-TIDP16-C213	Germany	Peter Buggisch Ifi - institut für interdisziplinäre medizin an der asklepios klinik st. georg Ifi-Studien und Projekte GmbH Hamburg 20246 Germany
TMC435-TIDP16-C213	Germany	Michael Biermer leber- und studienzentrum am checkpoint Charlottenstrasse 81 Berlin 10969 Germany
TMC435-TIDP16-C213	Germany	Dietmar Klass Universitätsklinikum Ulm Alberteinsteinallee 29 Ulm 89081 Germany
TMC435-TIDP16-C213	Great Britain	Queen Elizabeth Hospital Edgbaston Birmingham B15 2TH Great Britain
TMC435-TIDP16-C213	Great Britain	Institute Of Liver Studies, Kings College Hospital Denmark Hill London Se5 9rs Great Britain
TMC435-TIDP16-C213	Israel	Lady Davis Carmel Medical Center

		7 Michal Street Haifa 34362 Israel
TMC435-TIDP16-C213	Israel	Ziv Hospital Ziv Zefat Mc Zefat 13100 Israel
TMC435-TIDP16-C213	Italy	Azienda Ospedaliera Policlinico S. Orsola-Malpighi Via Massarenti 9 Bologna 40138 Italy
TMC435-TIDP16-C213	Mexico	Hospital Universitario de N.L. Av Madero Y Gonzalitos Ol Mitra Centro Monterrey 64460 Mexico
TMC435-TIDP16-C213	Netherlands	Academisch Medisch Centrum Meibergdreef 9 Amsterdam 1105 AZ Netherlands
TMC435-TIDP16-C213	Netherlands	Erasmus Mc Dr. Molewaterplein 40 Rotterdam 3015 CE Netherlands
TMC435-TIDP16-C213	New Zealand	Christchurch Hospital Private Bag 4710 Christchurch 8011 New Zealand
TMC435-TIDP16-C213	New Zealand	Auckland City Hospital 4 Ferncroft Street Auckland 1031 New Zealand
TMC435-TIDP16-C213	Poland	Wojewódzki Szpital Obserwacyjno-Zakaźny im. Tadeusza Browicza Bydgoszcz 85-030 Poland
TMC435-TIDP16-C213	Poland	Sp Zoz Wojewodzki Szpital Zespolony Oddzial Obserwacyjno-Zakazny Ul Radiowa 7 Kielce 25-317 Poland
TMC435-TIDP16-C213	Poland	Szpital Specjalistyczny, Oddzial Obserwacyjno-Zakazny Ul Zjednoczenia 10 Chorzow 41-500 Poland

TMC435-TIDP16-C213	Poland	Sp Zoz Wojewodzki Szpital Zakazny Warszawa 01-201 Poland
TMC435-TIDP16-C213	Poland	Id Clinic ul. Janowska 19 Myslowice 41-400 Poland
TMC435-TIDP16-C213	Portugal	Hospital Egas Moniz - Servicio De Doencas Infecto-Contagiosas Rua da Junqueira, 126 Lisboa 1349-019 Portugal
TMC435-TIDP16-C213	Portugal	Centro Hospitalar de Lisboa - Zona Central - Hospital de Santo António dos Capuchos Alameda De Santo Lisboa 1150-069 Portugal
TMC435-TIDP16-C213	Portugal	University Hospital of Coimbra Av.Bissaya Barreto 52 Coimbra 3041-853 Portugal
TMC435-TIDP16-C213	Romania	Institutul de Boli infectioase "Prof Dr Matei Bals" Str Dr Calistrat Grozovici Nr 1 Bucharest 021105 Romania
TMC435-TIDP16-C213	Russia	St. Petersburg Infectious Diseases Hospital #30 Mirgorodskaya Str 3 St Petersburg 193167 Russia
TMC435-TIDP16-C213	Russia	Smolensk Regional Clinical Hospital 27 Prospect Gagarina Street Smolensk 214018 Russia
TMC435-TIDP16-C213	Russia	Federl State Institution Republican Clinical Hospital 3 Shlisselburgskoe Shosse St Petersburg 196645 Russia
TMC435-TIDP16-C213	Russia	Saint-Petersburg City Center For Aids And Infectious Diseases Treatment And Prophylaxis 179 Obvodnoy Canal Saint-Petersburg 196645 Russia

TMC435-TIDP16-C213	Russia	Medical Company Hepatologist Oktyabrskaya str. 55 A Tolyaty 443063 Russia
TMC435-TIDP16-C213	Russia	State Health Care Institution Of Moscow City "City Clinical Hospital N. 64" Vavilova str., 61 Moscow 117292 Russia
TMC435-TIDP16-C213	Russia	Stavropol State Medical Academy Roszdrava Mira str., 310 Stavropol 355017 Russia
TMC435-TIDP16-C213	Russia	Institution Of Russian Academy Of Sciences Central Clinical Hospital Ran Fotievoy str., 12, bild. 3 Moscow 119333 Russia
TMC435-TIDP16-C213	Spain	Hospital Vall D'Hebron Paseo Vall d'Hebron 119-129 Barcelona 08035 Spain
TMC435-TIDP16-C213	Spain	Hospital Quiron De Valencia Paseo Blasco Ibánez 14 Valencia 46010 Spain
TMC435-TIDP16-C213	Spain	Hosp. Unv. de Valme Carretera De Cadiz S/n Km 548 9 Sevilla 41014 Spain
TMC435-TIDP16-C213	Ukraine	Vinnitsa National Medical University, Department of Internal Diseases 96 Khmelnitskoe Shosse Vinnitsa 21029 Ukraine
TMC435-TIDP16-C213	Ukraine	Donetsk National Medical University, Dept. of Internal Diseases 52A, Rosa Luksemburg Str Donetsk 83114 Ukraine
TMC435-TIDP16-C213	Ukraine	City Clinical Hospital N5 Kiev Center Prev & Treatm Of Aids 11,Vidpochynku Str Kyiv 03115 Ukraine

TMC435-TIDP16-C213	USA	Orlando Immunology Center N Mills Ave 1701 Orlando, FL 32803 USA
TMC435-TIDP16-C213	USA	The Office of Franco Felizarta San Dimas St 3535 Bakersfield,CA 93301 USA
TMC435-TIDP16-C213	USA	Liver Specialists Of Texas Fannin St Ste 1990 Houston,TX 77030 USA
TMC435-TIDP16-C213	USA	Ochsner Clinic Foundation Jefferson Hwy 1514 New Orleans, LA 70121 USA
TMC435-TIDP16-C213	USA	Baylor University Medical Center 3500 Gaston Ave Dallas, Texas 75246 USA
TMC435-TIDP16-C213	USA	Alamo Medical Research 621 Camden St Ste 202 San Antonio,Texas 78234 USA
TMC435-TIDP16-C213	USA	Cedars- Sinai Medical Center 8631 W 3Rd St Ste 430E Los Angeles,CA 90048 USA
TMC435-TIDP16-C213	USA	Fundacion De Investigacion De Diego 998 Munoz Rivera Avenue San Juan, PR 00927 USA
TMC435-TIDP16-C213	USA	University North Carolina 101, Manning Drive Chapel Hill, NC 27599 USA
TMC435-TIDP16-C213	USA	University of Pennsylvania 502 Johnson Pavilion Philadelphia, 19104 USA
TMC435-TIDP16-C213	USA	Digestive Health Specialists 589 Garfield St Ste 201 Tupelo, MS 38801

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TMC435-TIDP16-C213	USA	Borland-Groover Clinic 4800 Belfort Rd Ste 161 Jacksonville, FL 32256 USA
TMC435-TIDP16-C213	USA	Research And Education Inc 4141 Fairmount Avenue, Suite 201A San Diego,CA 92105 USA
TMC435-TIDP16-C213	USA	South Denver Gastroenterology, Pc-Hampden 499 East Hampden Avenue Englewood, 80113 USA

Changes in conduct

The original protocol dated 26 May 2011 was amended 5 times (28 June 2011, 10 January 2012, 20 April 2012, 18 April 2013 and 17 September 2013). Out of which only 3 amendments were considered as substantial amendments.

General Amendment

The global amendment to the protocol was amended on 10 January 2012, was considered substantial and was based on feedback from the Health Authorities on the revised C213 clinical trial protocol (CTP) of 28 June 2011 was integrated and following changes were made as a strong correlation between sustained virologic response (SVR) 12 weeks and 24 weeks was demonstrated in completed Simeprevir (SMV) Phase 2b studies (C205 and C206) and Health Authorities agreed that the primary efficacy endpoint for ongoing and future SMV Phase 3 studies could be changed from SVR24 to SVR12. SVR24 became a secondary endpoint. SVR definition was evaluated and updated, the thyroid function of the subjects should be adequately controlled and that subjects with abnormal thyroid-stimulating hormone (TSH) levels would be excluded, Specific management of pancreatic amylase or lipase elevations, gastrointestinal nausea (with or without vomiting) and diarrhea were deleted from the specific toxicities section, It was clarified that for all grades of rash, safety labs had to be taken and that subjects with a grade 3 or 4 rash had to discontinue all study treatment, International Conference on Harmonization (ICH) E2F guideline, reference to the Annual Safety Report was replaced by reference to the Development Safety Update Report, It was clarified that the Roche Cobas TaqMan HCV Test v2.0, for use with the High Pure System was used as the assay to determine hepatitis C virus (HCV) RNA levels, A liver biopsy inclusion criterion was added to the protocol, Nonclinical data showed that SMV induced a phototoxic response in BALB/c 3T3 cells. For that reason, precautionary language for photosensitivity had been added to the original C213 protocol, Additional tests for the urine dipstick analysis were listed,Female partners of male participants had to follow the guidelines on contraception as outlined in the manufacturer's prescribing information for ribavirin (RBV), Based on the results of study C116 SMV had to be administered with a meal and temporary interruption of SMV during the treatment period was allowed in the event of a suspected toxicity.

The global amendment to the protocol was amended on 18 April 2013, included the following changes to update the RGT duration criteria and the treatment stopping rules based on the Phase 3, The management of laboratory abnormalities and management of specific toxicities was updated and clarified based on the results from Phase 3 studies and based on results of drug-drug interaction studies, the section on prestudy and concomitant therapy was updated.

The global amendment to the protocol was amended on 17 September 2013, included the following changes Phase 1 photosensitivity study C125 had concluded that the photosensitizing potential of SMV is similar to that of placebo. Accordingly, formal recommendations for sun-protective measures were removed from the ongoing SMV studies at the time that these results became available, and not included in future SMV study protocols. As a follow-up to a recommendation by the United States (US) Food and Drug Administration (FDA), it was decided to reintroduce the same recommendations initially included in Phase 3 studies. Therefore, the protocol was amended to reintroduce the precautionary language on photosensitivity.

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