SYNOPSIS

Name of Sponsor/Company	Janssen Cilag International NV
Name of Investigational Product	TMC435 (simeprevir)

Status: Approved

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Prepared by: Janssen Infectious Diseases - Diagnostics BVBA

Protocol No.: TMC435HPC3014

Title of Study: A Phase 3, Open-Label Study to Evaluate the Safety and Efficacy of TMC435 plus Pegylated Interferon alfa-2a and Ribavirin Administered for 12 Weeks in Treatment-Naïve Subjects with Chronic Genotype 1 or Genotype 4 HCV Infection

EudraCT Number: 2012-004905-29

NCT No.:

Clinical Registry No.: 2012-004905-29

Coordinating Investigator(s): Tarik Asselah, MD

Study Centers: Austria (3 sites), Belgium (3 sites), France (4 sites), Germany (5 sites), Italy (5 sites) Saudi Arabia (3 sites), Spain (5 sites), United Kingdom (3 sites).

Publication (Reference): Not applicable

Study Period: 3 September 2013 to 31 August 2015

Phase of Development: 3b

Objectives:

Primary Objectives:

- To determine the efficacy of simeprevir (SMV) (previously known as TMC435) plus PegIFNα-2a and RBV when administered for 12 weeks in treatment-naïve subjects with chronic genotype 1 HCV infection, as measured by the proportion of subjects with sustained virologic response 12 weeks after the planned end of treatment (SVR12).
- To assess the safety and tolerability of SMV plus PegIFNα-2a and RBV when administered for 12 weeks in treatment-naïve subjects with chronic genotype 1 HCV infection.

Major Secondary Objectives:

- To determine the efficacy of SMV plus PegIFNα-2a and RBV when administered for 12 weeks in treatment-naïve subjects with chronic genotype 4 HCV infection, as measured by the proportion of subjects with SVR12.
- To assess the safety and tolerability of SMV plus PegIFNα-2a and RBV when administered for 12 weeks in treatment-naïve subjects with chronic genotype 4 HCV infection.

Further major secondary objectives in subjects with genotype 1 or genotype 4 HCV infection (separately per genotype) were:

- To determine the proportion of subjects who achieved virologic response at Week 2 (W2VR) and the proportion of subjects who achieved rapid virologic response (RVR).
- To determine the relationship between W2VR (HCV ribonucleic acid [RNA] <25IU/mL undetectable; HCV RNA <25IU/mL detectable; and combined) and SVR12 and between RVR and SVR12.
- To determine the efficacy of SMV plus PegIFNα-2a and RBV for 12 weeks followed by 12 weeks of PegIFNα-2a and RBV (ie, a total treatment duration of 24 weeks), as measured by the proportion of subjects with SVR12.
- To determine the efficacy of SMV plus PegIFNα-2a and RBV after a total treatment duration of 12 weeks, as measured by the proportion of subjects with sustained virologic response 24 weeks after planned end of treatment (SVR24).
- To determine the efficacy of SMV plus PegIFNα-2a and RBV for 12 weeks followed by 12 weeks of PegIFNα-2a and RBV (ie, a total treatment duration of 24 weeks), as measured by the proportion of subjects with SVR24.
- To evaluate the evolution of HCV RNA levels at regular intervals during treatment and after planned end of treatment.

and for both genotypes combined:

- To evaluate impact of HCV or its treatment on patient-reported symptoms and functioning using a new patient-reported outcomes tool, the Hepatitis C Symptom & Impact Questionnaire (HCV-SIQ) and four well-validated PRO instruments measuring severity and impact of fatigue (Fatigue Severity Scale, FSS), depressive symptoms (Center for Epidemiologic Studies Depression Scale, CES-D), time missed from work and impairment in daily activities (Work Productivity and Activity Impairment, WPAI: Hepatitis C), and health status (EuroQol 5 Dimension, EQ5D).

Methodology:

This multicenter, international study evaluated the efficacy, tolerability, and safety of 12-week triple therapy with SMV plus PegIFNα-2a and RBV in treatment-naïve adult subjects with genotype 1 or genotype 4 chronic HCV infection and fibrosis stage equivalent to F0-F2.

The study was conducted in 3 phases: a screening phase of maximum 6 weeks, a treatment phase extending from Day 1 (baseline) up to 12, 24 or 48 weeks depending on the response to treatment, and a posttreatment follow-up period of 24 weeks after the subject's last planned dose of study drug. The duration of the subject’s participation (excluding screening phase) varied between 36 weeks and 72 weeks, depending on the response to treatment. The study was considered completed with the last visit of the last subject.

All subjects started treatment at baseline (Day 1) and received triple therapy consisting of SMV plus PegIFNα-2a and RBV for 12 weeks. Total anti-HCV treatment duration was response-guided based on HCV RNA levels at Week 2, Week 4, and Week 8 as follows:

<u>For subjects with genotype 1 HCV infection:</u>

- subjects discontinued all anti-HCV treatment after Week 12 if HCV RNA value was
  - <25 IU/mL (detectable or undetectable) at Week 2

AND

  - <25 IU/mL undetectable at Week 4

AND

- <25 IU/mL undetectable at Week 8.

- If HCV RNA was above the threshold defined at any of the 3 time points, subjects continued PegIFNα-2a and RBV until Week 24.

For subjects with genotype 4 HCV infection:

- Subjects with host *IL28B* genotype CC qualified for a total treatment duration of only 12 weeks (ie, all anti-HCV treatment was discontinued after Week 12) if the following criteria were met: if HCV RNA value was

  - <25 IU/mL (detectable or undetectable) at Week 2

AND

  - <25 IU/mL undetectable at Week 4

AND

  - <25 IU/mL undetectable at Week 8.

- Subjects with host *IL28B* genotype CT or TT qualified for a total treatment duration of only 12 weeks (ie, all anti-HCV treatment was discontinued after Week 12) if the following criteria were met: if HCV RNA value was

  - <25 IU/mL undetectable at Week 2

AND

  - <25 IU/mL undetectable at Week 4

AND

  - <25 IU/mL undetectable at Week 8.

- For all host *IL28B* genotypes, if HCV RNA was above the threshold defined at any of the 3 time points, subjects stopped SMV treatment at Week 12 and continued PegIFNα-2a and RBV until Week 24.

The different algorithm used in subjects with genotype 4 HCV infection is the result of an urgent amendment of the protocol that was introduced after medical review of interim data. During this review, a high rate of relapse was observed in HCV genotype 1 subjects with *IL28B* genotype CT or TT who stopped treatment after 12 weeks and who had HCV RNA <25 IU/mL detectable at Week 2.

In subjects not meeting the above criteria for 12 weeks of treatment but with HCV RNA <25 IU/ml undetectable at week 4 (RVR), a total treatment duration of 24 weeks was recommended regardless of baseline response predictors. In subjects with HCV RNA <25 IU/ml detectable at Week 4, a total treatment duration of 24 weeks was also recommended. However, prolonged treatment duration of 48 weeks with PegIFNα-2a and RBV could be considered for certain subjects with HCV RNA <25 IU/mL detectable at Week 4, such as those with *IL28B* non-CC genotype. The decision to prolong total treatment to 48 weeks was taken at Week 20 at the investigator's discretion.

Regardless of treatment duration, endpoint to evaluate efficacy was SVR12.

The treatment continuation criteria could at all times be overruled if a subject met any of the virologic stopping criteria outlined below. Subjects meeting any of the following criteria were required to discontinue all treatment:

- Week 4: HCV RNA ≥25 IU/mL
- Week 12: HCV RNA ≥25 IU/mL OR <25 IU/mL detectable. HCV RNA <25 IU/mL detectable had to be confirmed if HCV RNA had been <25 IU/mL undetectable at an earlier time point.
- a confirmed increase of >1 $\log_{10}$ IU/mL in HCV RNA level from the lowest level reached, or a confirmed HCV RNA level of >100 IU/mL in subjects whose HCV RNA level had previously been <25 IU/mL while on study drugs.

Number of Subjects (planned and analyzed):

A target of 150 subjects infected with genotype 1 HCV and 75 subjects infected with genotype 4 HCV were planned to be assigned to treatment in this study.

In total, 277 subjects were screened, of whom 230 were randomized and treated (ITT population) (163 subjects with HCV genotype 1 and 67 subjects with HCV genotype 4). Two subjects were enrolled but not treated.

Subjects Screened, Enrolled, and Treated; All Subjects

	Genotype 1			Genotype 4			Genotype unknown	
	12 Weeks Treatment	>12 Weeks Treatment	All Subjects	12 Weeks Treatment	>12 Weeks Treatment	All Subjects	All Subjects	Total
Screened	-	-	183	-	-	89	5	277
Not enrolled	-	-	18	-	-	22	5	45
Enrolled but not treated	-	-	2	-	-	0	0	2
Enrolled and treated[a]	123	40	163	34	33	67	0	230
Completed SMV	122	29	151	34	28	62	0	213
Completed all study therapy	122	26	148	34	24	58	0	206
Study							0	
Completed	114	33	147	34	27	61		208
Discontinued	9	7	16	0	6	6	0	22

[a] Received at least one dose of study medication.

Diagnosis and Main Criteria for Inclusion:

Males or females aged between 18 and 70 years (extremes included); treatment-naïve with confirmed chronic HCV infection; liver biopsy performed within 2 years prior to screening or non-invasive confirmation of the liver disease stage (by transient elastography) performed within 6 months prior to screening; liver disease stage equivalent to METAVIR Score F0-F2 (no fibrosis, or portal fibrosis without or with few septa); genotype 1 or genotype 4 HCV infection (confirmed at screening). Subjects with liver disease stage equivalent to METAVIR Score F2 and without liver biopsy performed within 2 years prior to screening had to have undergone liver imaging within 6 months prior to the Screening visit (or between the Screening and Baseline/Day 1 visits) with no findings suspicious of hepatocellular carcinoma.

Subjects with advanced liver disease equivalent to METAVIR score F3-F4 (bridging fibrosis or cirrhosis), with hepatic decompensation, with any liver disease of non-HCV etiology, and/or with a non-genotype 1 or non-genotype 4 hepatitis C, hepatitis B or HIV co-infection were excluded. Subjects willing to participate, having signed the informed consent form (ICF), and found eligible for the study, were required to stop disallowed medication prior to starting treatment and were not to start disallowed medication during the study.

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

Simeprevir was taken as oral capsules at a once daily (qd) dose of 150 mg with food.

PegIFNα-2a and RBV were given as Pegasys® and Copegus®, respectively. Pegasys® and Copegus® were administered according to the manufacturer's prescribing information. Pegasys® (180 µg once weekly) was administered as weekly subcutaneous (SC) injections of 0.5 mL. If the subject's baseline body weight was <75 kg, the total daily dose of Copegus® was 1000 mg, administered as 400 mg (2 oral tablets of 200 mg, intake with food) in the morning and 600 mg (3 oral tablets of 200 mg, intake with food) in the evening. If the baseline body weight was ≥75 kg, the total daily dose was 1200 mg, administered as 600 mg in the morning and evening (3 oral tablets of 200 mg per intake, with food).

Simeprevir batch numbers: 4367530, 4368060, 4368467, 4368564, 4368992

Pegasys® batch numbers: 4367473, 4367820, 4368243, 4368562, 4368563, 4368565, 4369766

Copegus® batch numbers: 4367474, 4367475, 4367476, 4367749, 4368468, 4368484, 4368485, 4368569, 4368991, 4369765

Reference Therapy, Dose and Mode of Administration, Batch No.:

Not applicable

Efficacy Evaluations

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

Resistance Determinations

Samples for sequencing of HCV NS3/4A were collected at predefined time points. Sequencing of the baseline sample was done in real-time. Sequencing of samples taken after baseline occurred at the discretion of the Study Responsible Scientist.

Pharmacogenomic (DNA) Evaluations

A pharmacogenomic blood sample was collected to allow for host *IL28B* genotyping. This pharmacogenomic blood sample was mandatory and was collected from all subjects who consented to participate in the study.

Safety Evaluations

Safety and tolerability were evaluated throughout the study from signing of the informed consent form (ICF) onwards until the last study-related visit. Adverse events were reported from signing of ICF until 4 weeks after last intake of study medication. Thereafter, only AEs considered related to SMV were reported. Serious AEs (SAEs) were reported until 30 days after last study-related procedure. The evaluations of safety and tolerability included monitoring of AEs, clinical laboratory tests, vital signs, physical examination, hepatitis C symptoms and impact (HCV-SIQ), impact on work and daily activities (WPAI:Hepatitis C), health status and quality of life (EQ-5D), fatigue (FSS), and depressive symptoms (CES-D). Specific toxicity management plans were incorporated in line with known toxicities for the medicinal products evaluated in this study.

Statistical Methods

The primary analysis was performed when all subjects infected with genotype 1 HCV who were eligible for and assigned to a total treatment duration of 12 weeks had completed the Week 24 visit (SVR12) or discontinued earlier.

The final analysis was performed when all subjects had completed the last study-related visit (Week 36, Week 48, or Week 72 depending on total treatment duration) or discontinued earlier.

Efficacy

The primary efficacy endpoint was the proportion of subjects with SVR12, ie, subjects with undetectable HCV RNA (<25 IU/mL undetectable) at the actual end of treatment and 12 weeks after the planned end of treatment, in subjects infected with genotype 1 HCV who were eligible for and assigned to a total treatment duration of 12 weeks.

For the primary endpoint, SVR12 in subjects infected with genotype 1 HCV who were eligible for and assigned to 12 weeks of treatment, a one-sided test, with alpha=0.05 was used to compare the response rate to the protocol-defined minimally acceptable response rate of 80%. The z-statistic from the one-sample z-test for proportions was calculated under the null hypothesis of H0: P=P0 against the alternative hypothesis of H1: P>P0 (with P=the sample proportion of responders and P0=0.8).

Secondary efficacy parameters were analyzed as described below. Two-sided 95% confidence intervals were constructed around the observed response rate.

Secondary endpoints were:

In subjects infected with genotype 4 HCV who were eligible for and assigned to a total treatment duration of 12 weeks:

- the proportion of subjects with SVR12.

For all subjects per assigned total treatment duration and per HCV genotype (separately):

- the proportion of subjects who achieved RVR;
- the proportion of subjects who achieved virologic response at Week 2 (HCV RNA <25IU/mL undetectable; HCV RNA <25IU/mL detectable; and combined);
- the proportion of subjects with SVR12;
- the proportion of subjects with SVR24;
- the proportion of subjects with ≥2 log decrease in HCV RNA at each time point;
- the proportion of subjects with HCV RNA <25 IU/mL undetectable at each time point;
- the proportion of subjects with viral breakthrough;
- the proportion of subjects with viral relapse;
- the proportion of subjects with normalized ALT levels at the end of study and at time points SVR was assessed;
- change in liver disease stage assessment between screening assessment and assessment at SVR24 time point.

For all subjects per assigned total treatment duration and combined for both HCV genotypes:

- mean change from baseline at each study visit throughout treatment and follow-up for each of the PRO measures (HCV-SIQ symptom score, HCV impact score, FSS total score, CES-D score, WPAI missed work time, WPAI daily activity impairment, WPAI productivity score, EQ5D VAS, EQ5D valuation index, EQ5D Descriptive System scores).

Exploratory PRO endpoints

In subjects infected with genotype 1 or genotype 4 HCV for both genotypes combined:

- Mean change from baseline at each study visit throughout treatment and follow-up for the HCV-SIQ total score;
- Mean change from baseline at each study visit throughout treatment and follow-up for the HCV-SIQ symptom scores by body system.

Safety

Safety endpoints were analyzed in subjects infected with genotype 1 or genotype 4 HCV separately per genotype and for both genotypes combined:

Adverse Events: The verbatim terms used in the CRF by investigators to identify AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0. All reported AEs with onset during the treatment phase (ie, treatment-emergent AEs, and AEs that have worsened since baseline) were included in the analysis. For each AE, the percentage of subjects who experienced at least 1 occurrence of the given event was summarized by treatment group. Summaries, listings, datasets, or subject narratives could be provided, as appropriate, for those subjects who died, who discontinued treatment due to an AE, or who experienced a severe or an SAE.

Clinical Laboratory Tests: Laboratory data were summarized by type of laboratory test. Descriptive statistics (actual values and changes from reference) were calculated for each laboratory analyte at baseline and 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) values and changes from baseline were summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits were summarized.

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

RESULTS:

STUDY POPULATION

	Genotype 1			Genotype 4		
	12 Weeks Treatment	>12 Weeks Treatment	All Subjects	12 Weeks Treatment	>12 Weeks Treatment	All Subjects
Trial						
N	123	40	163	34	33	67
Completed	114 (92.7%)	33 (82.5%)	147 (90.2%)	34 (100.0%)	27 (81.8%)	61 (91.0%)
Discontinued	9 (7.3%)	7 (17.5%)	16 (9.8%)		6 (18.2%)	6 (9.0%)
Lost to follow-up	5 (4.1%)	2 (5.0%)	7 (4.3%)		3 (9.1%)	3 (4.5%)
Other	1 (0.8%)		1 (0.6%)			
Subject entered another investigational trial	2 (1.6%)	1 (2.5%)	3 (1.8%)			
Subject non-compliant					1 (3.0%)	1 (1.5%)
Withdrawal by subject	1 (0.8%)	4 (10.0%)	5 (3.1%)		2 (6.1%)	2 (3.0%)
Completed all study therapy[a]	122 (99.2%)	26 (65.0%)	148 (90.8%)	34 (100.0%)	24 (72.7%)	58 (86.6%)
Completed Simeprevir	122 (99.2%)	29 (72.5%)	151 (92.6%)	34 (100.0%)	28 (84.8%)	62 (92.5%)
Completed PR[b]	123 (100.0%)	27 (67.5%)	150 (92.0%)	34 (100.0%)	24 (72.7%)	58 (86.6%)
During the SMV + PR phase[c]						
Discontinued RBV and PegIFN					1 (3.0%)	1 (1.5%)
Discontinued Simeprevir and RBV	1 (0.8%)		1 (0.6%)			
Discontinued Simeprevir only		1 (2.5%)	1 (0.6%)			
Discontinued all study therapy		10 (25.0%)	10 (6.1%)		5 (15.2%)	5 (7.5%)
During the PR only phase[c]						
Discontinued RBV and PegIFN		3 (7.5%)	3 (1.8%)		3 (9.1%)	3 (4.5%)
Discontinued RBV only		1 (2.5%)	1 (0.6%)			

[a] Subjects who completed all study therapy
[b] Subjects who completed at least one study drug (RBV or PegIFN)
[c] In case the stopping rule at Week 12 was met, it was possible that the actual discontinuation of PR occurred during the PR only phase, and not during the SMV + PR phase

In the genotype 1 group, 42.9% of subjects were female, the median age was 47.0 years (range: 23; 68 years), and the median body mass index (BMI) was 25.10 kg/m^2 (range: 15.7; 38.9 kg/m^2). Of the 140 subjects for which local regulations allowed gathering data on race and ethnicity, 92.2% were white, and 97.9% were not of Hispanic or Latino ethnicity.

In the genotype 4 group, 31.3% of subjects were female, the median age was 48.0 years (range: 19; 66 years), and the median BMI was 26.30 kg/m^2 (range: 18.4; 35.8 kg/m^2). Of the 59 subjects for which

local regulations allowed gathering data on race and ethnicity, 79.7% were white, and 98.3% were not of Hispanic or Latino ethnicity.

In the genotype 1 group, the median HCV RNA level at baseline was 6.48 log_{10} IU/mL (range: 3.7; 7.7 log_{10} IU/mL). The majority of subjects (77.9%) had high baseline plasma HCV RNA levels, defined as plasma HCV RNA >800,000 IU/mL. Sixty-seven subjects (41.1%) were infected with HCV genotype 1a, of whom 11 subjects had Q80K polymorphism at baseline (6.9% of subjects with sequencing data). Ninety-six subjects (58.9%) were infected with HCV genotype 1b (of whom none had Q80K polymorphism at baseline). At baseline, increased ALT (any grade) was observed in 56.4% of the subjects, mainly grade 1 (44.2%). The median time since diagnosis of HCV infection was 4.40 years (range: 0.4; 28.9 years). There was a tendency towards lower median baseline log_{10} HCV RNA in subjects with a treatment duration of 12 weeks (6.26 log_{10} IU/mL [range: 3.7; 7.7 log_{10} IU/mL]) than in subjects in the >12 weeks treatment group (6.62 log_{10} IU/mL [range: 5.2; 7.4 log_{10} IU/mL]). The proportion of subjects with baseline HCV RNA >800.000 IU/mL was also lower in subjects with a treatment duration of 12 weeks (73.2%) than in subjects in the >12 weeks treatment group (92.5%).

In the genotype 4 group, the median HCV RNA level at baseline was 6.09 log_{10} IU/mL (range: 3.1; 7.5 log_{10} IU/mL). The majority of subjects (61.2%) had high baseline plasma HCV RNA levels, defined as plasma HCV RNA >800,000 IU/mL. Twenty-seven subjects (40.3%) were infected with HCV genotype 4a, 25 subjects with HCV genotype 4d (37.3%) and 15 subjects (22.4%) with another genotype 4 HCV subtype (4other). No subject infected with HCV genotype 4 had Q80K polymorphism at baseline. At baseline, increased ALT (any grade) was observed in 35.8% of the subjects, mainly grade 1 (22.4%). The median time since diagnosis of HCV infection was 6.10 years (range: 0.5; 26.3 years). There was a tendency towards lower median baseline log_{10} HCV RNA in subjects with a treatment duration of 12 weeks (5.81 log_{10} IU/mL [range: 3.1; 7.5 log_{10} IU/mL]) than in subjects in the >12 weeks treatment group (6.40 log_{10} IU/mL [range: 4.8; 7.2 log_{10} IU/mL]). The proportion of subjects with baseline HCV RNA >800.000 IU/mL was also lower in subjects with a treatment duration of 12 weeks (44.1%) than in subjects in the >12 weeks treatment group (78.8%).

	Genotype 1			Genotype 4		
	12 Weeks Treatment	>12 Weeks Treatment	All Subjects	12 Weeks Treatment	>12 Weeks Treatment	All Subjects
Demographic Characteristics						
Analysis set: intent-to-treat	123	40	163	34	33	67
Gender						
N	123	40	163	34	33	67
Female	58 (47.2%)	12 (30.0%)	70 (42.9%)	11 (32.4%)	10 (30.3%)	21 (31.3%)
Male	65 (52.8%)	28 (70.0%)	93 (57.1%)	23 (67.6%)	23 (69.7%)	46 (68.7%)
Age (years)						
N	123	40	163	34	33	67
Mean (SD)	45.4 (10.57)	48.2 (9.70)	46.1 (10.40)	43.6 (13.87)	46.4 (11.19)	45.0 (12.60)
Median	47.0	49.5	47.0	47.5	48.0	48.0
Range	(23; 68)	(26; 64)	(23; 68)	(19; 63)	(21; 66)	(19; 66)
Race						
Not allowed to ask per local regulations	16	7	23	4	4	8
N	107	33	140	30	29	59
Asian	3 (2.8%)	0	3 (2.1%)	2 (6.7%)	1 (3.4%)	3 (5.1%)
Black or African American	5 (4.7%)	1 (3.0%)	6 (4.3%)	3 (10.0%)	4 (13.8%)	7 (11.9%)
Multiple	0	0	0	2 (6.7%)	0	2 (3.4%)

	Genotype 1			Genotype 4		
	12 Weeks Treatment	>12 Weeks Treatment	All Subjects	12 Weeks Treatment	>12 Weeks Treatment	All Subjects
Native Hawaiian or Other Pacific Islander	1 (0.9%)	0	1 (0.7%)	0	0	0
White	98 (91.6%)	32 (97.0%)	130 (92.9%)	23 (76.7%)	24 (82.8%)	47 (79.7%)
Body mass index (kg/m²)						
N	123	40	163	34	33	67
Mean (SD)	25.44 (4.384)	25.36 (4.138)	25.42 (4.312)	25.00 (4.056)	27.68 (3.878)	26.32 (4.163)
Median	25.10	25.45	25.10	24.60	27.50	26.30
Range	(16.6; 38.9)	(15.7; 33.9)	(15.7; 38.9)	(18.4; 32.9)	(19.0; 35.8)	(18.4; 35.8)
Baseline Disease Characteristics						
Baseline log_{10} HCV RNA level						
N	123	40	163	34	33	67
Mean (SD)	6.26 (0.713)	6.62 (0.503)	6.35 (0.684)	5.82 (0.825)	6.27 (0.532)	6.05 (0.727)
Median	6.38	6.65	6.48	5.81	6.40	6.09
Range	(3.7; 7.7)	(5.2; 7.4)	(3.7; 7.7)	(3.1; 7.5)	(4.8; 7.2)	(3.1; 7.5)
Baseline HCV RNA level (IU/mL)						
N	123	40	163	34	33	67
<400000 IU/mL	21 (17.1%)	2 (5.0%)	23 (14.1%)	11 (32.4%)	3 (9.1%)	14 (20.9%)
≥400000 - ≤800000 IU/mL	12 (9.8%)	1 (2.5%)	13 (8.0%)	8 (23.5%)	4 (12.1%)	12 (17.9%)
>800000 IU/mL	90 (73.2%)	37 (92.5%)	127 (77.9%)	15 (44.1%)	26 (78.8%)	41 (61.2%)
HCV geno/subtype						
N	123	40	163	34	33	67
1a	49 (39.8%)	18 (45.0%)	67 (41.1%)	0	0	0
1b	74 (60.2%)	22 (55.0%)	96 (58.9%)	0	0	0
4a	0	0	0	14 (41.2%)	13 (39.4%)	27 (40.3%)
4d	0	0	0	13 (38.2%)	12 (36.4%)	25 (37.3%)
4other	0	0	0	7 (20.6%)	8 (24.2%)	15 (22.4%)
Il28b genotype as stratified						
N	123	40	163	34	33	67
CC	32 (26.0%)	8 (20.0%)	40 (24.5%)	14 (41.2%)	1 (3.0%)	15 (22.4%)
CT	73 (59.3%)	20 (50.0%)	93 (57.1%)	15 (44.1%)	27 (81.8%)	42 (62.7%)
TT	18 (14.6%)	12 (30.0%)	30 (18.4%)	5 (14.7%)	5 (15.2%)	10 (14.9%)

EFFICACY RESULTS:

Primary Efficacy Endpoint

The primary efficacy endpoint was the comparison of the response rate (ie, proportion of subjects with SVR12) in the genotype 1 subjects who received a 12-week treatment with the protocol-defined minimally acceptable response rate of 80%.

The rate (95% CI) of subjects with SVR12 in genotype 1 subjects with a treatment duration of 12 weeks was 65.9% (57.47; 74.23%). Results of the one-sided Z-test did not allow to reject the H0 hypothesis, meaning that it could not be concluded that the SVR12 rate was higher than the minimally acceptable rate of 80%.

For the ITT population, in the genotype 1 group, 123 subjects (75.5%) met the response-guided treatment (RGT) criteria and were eligible for a total treatment duration of 12 weeks. The remaining 40 subjects (24.5%) were allocated to the >12 weeks treatment duration group because they did not meet the RGT criteria or were unclassifiable due to early discontinuation. In the genotype 4 group, 34 subjects (50.7%) and 33 subjects (49.3%) were allocated to the 12 weeks treatment duration group and >12 weeks treatment duration group, respectively.

In the genotype 1 group, SVR12 (95% CI) rates were 65.9% (57.47; 74.23%) in subjects with a treatment duration of 12 weeks and 52.5% (37.02; 67.98%) for subjects in the >12 weeks treatment duration group.

In the genotype 4 group, SVR12 (95% CI) rates were 97.1% (91.38; 100.0%) in subjects with a treatment duration of 12 weeks and 81.8% (68.66; 94.98%) for subjects in the >12 weeks treatment duration group.

Primary Analysis: z-test for Comparison of Observed SVR12 Rate with the Minimally Acceptable Response Rate, in Subjects with Genotype 1 HCV Infection and with a Planned Treatment Duration of 12 Weeks; Intent-to-treat

Simeprevir 12Wks 150 mg PR12/24			
SVR12 Rate		One-sample One-sided Z-test [a]	
n/N (%)	95% CI	Z-statistic [b]	p-value
81/123 (65.9)	(57.47; 74.23)	-3.92	1.0000

[a] One-sided one-sample Z-test for proportions comparing the observed SVR12 rate to the minimally acceptable response rate (=80%) when treated for 12 Weeks.
[b] The Z-statistic was calculated under the null hypothesis of H0: P=P0 against the alternative hypothesis of H1: P>P0 where P0 was 80%.

Primary Endpoint: Sustained Virologic Response 12 Weeks After the Planned End of Treatment (SVR12); Intent-to-treat

	Genotype 1			Genotype 4		
	12 Weeks Treatment	>12 Weeks Treatment	All Subjects	12 Weeks Treatment	>12 Weeks Treatment	All Subjects
Analysis set: intent-to-treat	123	40	163	34	33	67
SVR12						
Yes						
n/N (%)	81/123 (65.9%)	21/40 (52.5%)	102/163 (62.6%)	33/34 (97.1%)	27/33 (81.8%)	60/67 (89.6%)
95% CI	(57.47; 74.23)	(37.02; 67.98)	(55.15; 70.01)	(91.38; 100.00)	(68.66; 94.98)	(82.23; 96.88)

There were no relevant differences in SVR12 rates between subjects infected with HCV genotype 1a and subjects infected with HCV genotype 1b. The same was observed when comparing subjects infected with HCV genotype 4a and subjects infected with HCV genotype 4b or subjects infected with another HCV genotype 4 subtype (4other). There was a trend towards better SVR12 rates in subjects with *IL28B* genotype CC as compared to subjects with *IL28B* genotype CT or TT.

In the genotype 1 group, SVR12 was achieved by 8 of the 11 subjects (72.7%) with Q80K polymorphism at baseline and by 90 of the 148 subjects (60.8%) without Q80K polymorphism at baseline. None of the subjects in the genotype 4 group had Q80K polymorphism at baseline.

For the ITT population, in the genotype 1 group, SVR4 (95% CI) rates were 88.6% (83.01; 94.23%) in subjects with a treatment duration of 12 weeks and 60.0% (44.82; 75.18%) for subjects in the >12 weeks treatment duration group. SVR24 (95% CI) rates were 64.2% (55.76; 72.70%) in subjects with a treatment duration of 12 weeks and 52.5% (37.02; 67.98%) for subjects in the >12 weeks treatment duration group.

In the genotype 4 group, SVR4 (95% CI) rates were 100.0% (100.0; 100.0%) in subjects with a treatment duration of 12 weeks and 87.9% (76.74; 99.01%) for subjects in the >12 weeks treatment duration group. SVR24 (95% CI) rates were 97.1% (91.38; 100.00%) in subjects with a treatment duration of 12 weeks and 81.8% (68.66; 94.98%) for subjects in the >12 weeks treatment duration group.

In the genotype 1 group, 3 subjects who achieved SVR12 did not achieve SVR24. All 3 subjects were treated for 12 weeks and experienced viral relapse after the SVR12 time point. One subject achieved SVR24 but did not achieve SVR12. This subject experienced viral relapse (confirmed by an additional sampling) between the end of treatment and the SVR12 time point. At time of relapse, the subject had HCV RNA <25 IU/mL detectable and 7 days later, HCV RNA was 16,600 IU/mL. At the time point of SVR24 the subject had HCV RNA <25 IU/mL detectable. The subject was considered as having achieved SVR24 since the last assessment in the study was <25 IU/mL and no further assessment was available.

In the genotype 4 group, all subjects who achieved SVR12 also achieved SVR24.

In the genotype 1 group, SVR12 was not achieved in 61 subjects (37.4%) in total, 42/123 subjects (34.1%) with a treatment duration of 12 weeks, and 19/40 subjects (47.5%) in the >12 weeks treatment duration group. The proportion of subjects with on-treatment failure was 6.1% (10 subjects). All subjects with on-treatment failure discontinued at least 1 study drug (8 because they met a virologic stopping rule and 2 due to an AE). Of the 10 subjects with on-treatment failure (all assigned per protocol to the >12 weeks treatment duration group), 7 subjects (4.3%) failed due to meeting a stopping rule at Week 4, 2 subjects (1.2%) due to other reasons, and 1 subject (0.6%) due to viral breakthrough.

One subject met a stopping rule at Week 4 but continued treatment. The subject experienced viral relapse at Week 12. At the time treatment was discontinued (Week 10), the subject had undetectable HCV RNA and was thus not considered as on-treatment failure. Including this specific subject, 9 subjects (5.5%, all assigned per protocol to the >12 weeks treatment duration group) met any stopping rule (including stopping rule at Week 4, Week 12, and viral breakthrough). Four subjects (2.5%, all assigned per protocol to the >12 weeks treatment duration group) experienced viral breakthrough. Three of these subjects had viral breakthrough during SMV+PR treatment and 1 during PR only treatment. Three of the 4 subjects with viral breakthrough also met a virologic stopping rule at Week 4.

Post-treatment failure (including subjects who achieved SVR12 and relapsed thereafter) was observed in 54 subjects (33.1%): 45 subjects (36.6%) with a treatment duration of 12 weeks (3 [2.4%] due to missing value at time of SVR12 and 42 [34.1%] due to viral relapse) and 9 subjects (22.5%) in the >12 weeks treatment duration group (all due to viral relapse). Three subjects (all with a treatment duration of 12 weeks) experienced viral relapse after having achieved SVR12.

Fifty-one subjects (33.6%) experienced viral relapse (42 subjects [34.4%] with a treatment duration of 12 weeks and 9 subjects [30.0%] in the >12 weeks treatment duration group).

In the subjects with a treatment duration of 12 weeks, 41 of the 42 subjects with viral relapse completed all treatment and 1/42 completed PegIFNα-2a treatment and discontinued SMV and RBV. The majority of subjects who relapsed did so in the first 4 weeks after end of treatment (12 subjects, 9.8%) or between Week 4 and Week 12 after end of treatment (26 subjects, 23.9%).

For subjects in the >12 weeks treatment duration group, 6 of the 9 subjects with viral relapse completed all treatment, 2 discontinued all treatments, and 1 discontinued PegIFNα-2a/RBV treatment but

completed SMV treatment. All the subjects who relapsed did so in the first 12 weeks after end of treatment (4 subjects in the first 4 weeks and 5 subjects between Week 4 and Week 12).

In the genotype 4 group, SVR12 was not achieved in 7 subjects (10.4%) in total: 1/34 subject (2.9%) with a treatment duration of 12 weeks, and 6/33 subjects (18.2%) in the >12 weeks treatment duration group. The proportion of subjects with on-treatment failure was 4.5% (3 subjects). All subjects with on-treatment failure discontinued at least 1 study drug (2 due to meeting a virologic stopping rule and 1 due to other reasons). Of the 3 subjects with on-treatment failure (all assigned per protocol to the >12 weeks treatment duration group), 2 subjects (3.0%) failed due to meeting a virologic stopping rule and 1 subject (1.5%) failed due to another reason.

Two subjects (3.0%, all assigned per protocol to the >12 weeks treatment duration group) met a virologic stopping rule at Week 4.

One subject (1.5%, assigned per protocol to the >12 weeks treatment duration group) experienced viral breakthrough. This subject had viral breakthrough during SMV+PR treatment, and also met a virologic stopping rule at Week 4.

Four subjects (6.3%) experienced viral relapse (1 subject [2.9%] with a treatment duration of 12 weeks and 3 subjects [10.0%] in the >12 weeks treatment duration group).

Three of the 4 subjects with viral relapse completed all treatment, and 1 discontinued all treatment. All the subjects who relapsed did so in the first 12 weeks after end of treatment (1 subject in the first 4 weeks and 3 subjects between Week 4 and Week 12).

In the majority of genotype 1 infected subjects who did not achieve SVR12 and had paired baseline and failure sequencing data available, emerging mutations at NS3 positions 80, 155, or 168 were detected at time of failure.

SAFETY RESULTS:

Safety results are presented for genotype 1 and genotype 4 subjects together.

Adverse Events

No death occurred during the study.

During the entire treatment phase, 8 subjects (3.5%) experienced an SAE. Five subjects (2.2%) experienced an SAE during the SMV+PR phase. These SAEs were: grade 3 pericoronitis (recovered), grade 2 furuncle (recovered), grade 3 alcohol withdrawal syndrome (recovered with sequelae), grade 2 acute sinusitis (recovered), and grade 2 phlebitis (recovered). Each SAE occurred in at most 1 of the 8 subjects. Three subjects (4.8%) experienced an SAE during the PR only phase. These SAEs were: grade 3 testicular necrosis (recovered), grade 3 rash (recovered), and grade 3 psychotic disorder (recovery status unknown). Each SAE occurred in at most 1 of the 3 subjects.

One SAE (grade 3 rash) was considered possibly related to SMV by the investigator. This AE was reported on Day 141 (PR only phase) and was considered possibly related to SMV, RBV, and PegIFNα-2a by the investigator. Ribavirin and PegIFNα-2a were permanently discontinued due to this SAE. The SAE resolved after 10 days.

During the SMV+PR phase, 92.6% of the subjects experienced at least 1 AE. Most AEs were grade 1 or 2 in severity. Grade 3 and 4 AEs were reported in 17.8% and 3.5% of subjects, respectively. Adverse events that led to discontinuation of all study medication occurred in 6 subjects (2.6%).

Only neutropenia was reported as a grade 3 or 4 AE in >5% of subjects (10.4% of subjects).

During the SMV+PR phase, AEs considered at least possibly related to SMV by the investigator were reported in 48.7% of subjects. The most frequently reported of these AEs (in >10% of subjects) were pruritus (14.3% of subjects) and fatigue (13.5% of subjects). When considering the entire treatment phase, rash was reported in 10.4% of the subjects. Grade 3 AEs considered at least possibly related to SMV by the investigator were reported in 4.3% of subjects. No grade 4 AEs were considered at least possibly related to SMV by the investigator.

Simeprevir was permanently discontinued (along with PegIFNα-2a and RBV) due to an AE in 6 subjects (2.6%): 1 due to grade 4 dyspnea, 1 due to grade 1 pyrexia, 1 due to grade 2 urinary incontinence, 1 due to grade 2 pruritus, 1 due to grade 3 depression, and 1 due to grade 2 pyrexia, grade 2 oropharyngeal pain, grade 3 headache, and grade 1 abdominal pain. Among these AEs, grade 2 urinary incontinence and grade 2 pruritus were considered at least possibly related to SMV. Note that by protocol, all study medication had to be discontinued if the subject experienced a grade 4 AE, regardless of the relation to study medication.

Some AEs were of special or clinical interest. Increased bilirubin was considered an AE of special interest and rash (any type), pruritus, anemia, photosensitivity conditions, neutropenia, and dyspnea events were considered AEs of clinical interest. During the SMV+PR phase, increased bilirubin was reported in 6.5% of subjects, rash (any type) events in 19.6% of subjects, pruritus events in 29.6% of subjects, anemia events in 12.2% of subjects, photosensitivity conditions events in 0.4% of subjects, neutropenia events in 22.2% of subjects, and dyspnea events in 12.6% of subjects. Most of these events were grade 1 or 2 in severity. One dyspnea event (grade 4) led to discontinuation of all study medication. One grade 3 rash was considered an SAE and led to discontinuation of PegIFN/RBV treatment. These events of special/clinical interest were considered at least possibly related to SMV in 5.7% of subjects for increased bilirubin events, 13.0% for rash events (any type), 14.8% for pruritus events, 1.7% for anemia events, 0.4% for photosensitivity conditions events, 0.9% for neutropenia events, and 3.5% for dyspnea events.

	SMV+PR Phase	PR Only Phase	Entire Treatment Phase
Analysis set: Intent-to-treat	230	62	230
Any AE	213 (92.6%)	40 (64.5%)	214 (93.0%)
Most frequent AEs by PT[c], n (%)			
Influenza like illness	69 (30.0%)	3 (4.8%)	71 (30.9%)
Fatigue	58 (25.2%)	1 (1.6%)	59 (25.7%)
Pruritus	67 (29.1%)	3 (4.8%)	71 (30.9%)
Asthenia	56 (24.3%)	1 (1.6%)	57 (24.8%)
Headache	50 (21.7%)	3 (4.8%)	54 (23.5%)
Any AE with fatal outcome	0	0	0
Any SAE	5 (2.2%)	3 (4.8%)	8 (3.5%)
Worst grade 3 or 4 AE	49 (21.3%)	6 (9.7%)	54 (23.5%)
AE leading to permanent stop[a]			
SMV[b]	6 (2.6%)	0	6 (2.6%)
SMV only	0	0	0
SMV, PegIFNα-2a and RBV	6 (2.6%)	0	6 (2.6%)
PegIFNα-2a or RBV only	0	2 (3.2%)	2 (0.9%)

[a] Permanent stop of at least one drug.
[b] Without regard to PegIFNα-2a and RBV.
[c] During the first 12 weeks and in >20% of subjects
Allocation of an AE that led to permanent stop of study drug(s) to a treatment phase was based on the onset date of the AE.

Clinical Laboratory Evaluation

No relevant mean changes over time in laboratory parameters were observed.

During the SMV+PR phase, the most frequent (ie, >25% of subjects) graded treatment-emergent laboratory abnormalities (with worst treatment-emergent laboratory WHO toxicity grade ≥3) were neutrophils and precursors decreased (72.8%, any grade), and hyperbilirubinemia (42.1%, any grade).

During the first 12 weeks, in the combined SMV/PR arms, the most frequent (ie, >25% of subjects) non-graded treatment emergent laboratory abnormalities (below or above normal range) were leukocytes below (82.5%), neutrophils segmented below (81.6%), erythrocytes below (72.4%), hematocrit below (48.2%), neutrophils, segmented/leukocytes below (44.4%), lymphocytes/leukocytes above (40.4%), lymphocytes below (37.3%), cholesterol below (36.4%), lactate dehydrogenase above (33.8%), LDL cholesterol below (30.7%), erythrocytes mean corpuscular volume above (31.6%), and monocytes/leukocytes above (27.2%).

Other safety observations

During the SMV+PR phase, treatment-emergent abnormalities in vital signs were reported in <10% of subjects except for grade 1 SBP increased, reported in 12.3% of subjects. Most abnormalities were grade 1 or 2 in severity.

PATIENT-REPORTED OUTCOMES

For all PRO endpoints, clinically important worsening in scores was observed during the first 12 weeks of treatment. Thereafter, mean scores rapidly returned to baseline values in subjects that stopped all treatments at Week 12. For subjects in the >12 weeks treatment duration group, mean scores slowly improved after Week 12 and returned rapidly to baseline after all treatments were stopped.

STUDY LIMITATIONS:

No notable study limitations were identified by the sponsor.

CONCLUSION(S):

This multicenter, international study evaluated the efficacy, tolerability, and safety of 12-week triple therapy with SMV plus PegIFNα-2a and RBV in treatment-naïve adult subjects with genotype 1 or genotype 4 chronic HCV infection and fibrosis stage equivalent to F0-F2.

All subjects received triple therapy consisting of SMV plus PegIFNα-2a and RBV for 12 weeks. Total anti-HCV treatment duration was response-guided based on HCV RNA levels at Week 2, Week 4, and Week 8. Subjects with genotype 4 HCV had more strict RGT criteria than subject with genotype 1 HCV as result of an urgent amendment of the protocol that was introduced after medical review of interim data. During this review, a high rate of relapse was observed in HCV genotype 1 subjects with IL28B genotype CT or TT who stopped treatment after 12 weeks and who had HCV RNA <25 IU/mL detectable at Week 2.

The rate (95% CI) of subjects with SVR12 in genotype 1 subjects was 65.9% (57.47; 74.23%) for subjects with a treatment duration of 12 weeks and 52.5% (37.02; 67.98%) for subjects in the >12 weeks treatment duration group. Statistical analysis showed that the SVR12 rate in genotype 1 subjects who received 12 weeks was not higher than the minimally acceptable rate of 80%.

In the genotype 4 group, with more stringent RGT criteria, SVR12 (95% CI) rates were 97.1% (91.38; 100.0%) in subjects with a treatment duration of 12 weeks and 81.8% (68.66; 94.98%) for subjects in the >12 weeks treatment duration group. These results should be interpreted taking into account the smaller sample size as well as the amendment that modified the RGT criteria for subjects with HCV genotype 4 infection, resulting in a higher proportion of subjects receiving treatment for >12 weeks.

In the genotype 1 group, SVR12 was achieved by 8 of the 11 subjects (72.7%) with Q80K polymorphism at baseline and by 90 of the 148 subjects (60.8%) without Q80K polymorphism at baseline. None of the subjects in the genotype 4 group had Q80K polymorphism at baseline.

Treatment with SMV, PegIFNα-2a, and RBV was generally safe and well tolerated. Patient-reported outcomes showed that treatment-induced worsening in quality of life resolved upon treatment completion.

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