SYNOPSIS

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

Status: Approved
Date: 1 December 2015
Prepared by: Janssen-Cilag International NV

Protocol No.: TMC435HPC2014

Title of Study: A Phase 2a, Partly Randomized, Open-label Trial to Investigate the Efficacy and Safety of an 8- or 12-Week Treatment Regimen of Simeprevir in Combination With Sofosbuvir in Treatment-Naïve and -Experienced Subjects With Chronic Genotype 4 Hepatitis C Infection

Study Name: OSIRIS (Optimize Simeprevir In a Regimen Including Sofosbuvir)

NCT No.: NCT02278419

Clinical Registry No.: CR104970

Coordinating Investigator: [redacted], MD, MBBS, MB BCh, [redacted], Egypt

Study Centers: This study was conducted at 3 sites in Egypt.

Publications (References):

- El Raziky M, Gamil M, Hammad R, et al. A phase IIa, partly randomized, open-label trial of simeprevir combined with sofosbuvir for the treatment of HCV genotype 4-infected patients with or without cirrhosis (OSIRIS). Presented at the annual meeting of the European Association for the Study of the Liver, Vienna, Austria, 22-26 April 2015.
- El Raziky M, Gamil M, Hammad R, et al. Treatment of hepatitis C genotype 4 patients with simeprevir and sofosbuvir: preliminary results from a phase IIa, partially randomised, open-label trial conducted in Egypt (OSIRIS). Presented at the annual meeting of the American Association for the Study of Liver Diseases, San Francisco, California, USA, 13-17 November 2015.

Study Period: 07 December 2014 to 31 August 2015 (cutoff date for this analysis)

Phase of Development: 2a

Objectives:

The primary objective was to evaluate the efficacy of simeprevir (150 mg once daily) in combination with sofosbuvir (400 mg once daily) for 8 or 12 weeks versus a historical control, with respect to the percentage of subjects with sustained virologic response (SVR) 12 weeks after the end of treatment (EOT) (SVR12) in the overall population (Groups A1 [8 weeks; without cirrhosis], A2 [12 weeks; without cirrhosis], and B [12 weeks; with cirrhosis] combined).

The secondary objectives listed below include analysis of SVR 24 weeks after EOT (SVR24). Because most subjects had not reached the end of the study (24 weeks after EOT) at data cutoff for this analysis, SVR24 data are not presented in this report. The secondary objectives were:

- To evaluate the efficacy of 8-week or 12-week double-combination regimen of simeprevir in combination with sofosbuvir with respect to the percentage of subjects with SVR 4 weeks after EOT (SVR4) and SVR24 in the overall population (Groups A1, A2, and B combined).
- To estimate the relative efficacy (SVR12 and SVR24) of 8 weeks (Group A1) versus 12 weeks (Group A2) of simeprevir in combination with sofosbuvir in subjects with hepatitis C (HCV) genotype 4 without cirrhosis.
- To evaluate the on-treatment virologic responses of simeprevir in combination with sofosbuvir at all time points.
- To investigate the safety and tolerability of an 8-week or 12-week double combination regimen of simeprevir in combination with sofosbuvir.
- To evaluate the frequency of on-treatment failures, including viral breakthrough.
- To evaluate the frequency of viral relapse.

Methodology: This was a partially randomized, open-label, multicenter, Phase 2a study conducted in Egypt to evaluate the efficacy and safety of 8 and 12 weeks of simeprevir (150 mg once daily) in combination with sofosbuvir (400 mg once daily) in subjects chronically infected with HCV genotype, 4 who were treatment naïve or treatment experienced and had compensated liver disease.

The study consisted of a screening phase of up to 4 weeks, an open-label treatment phase of 8 weeks or 12 weeks, and a posttreatment follow-up phase until 24 weeks after EOT. An extension of the screening phase for up to 6 weeks was permitted for subjects who required a liver biopsy. The duration of the subjects' participation, including the screening phase, was approximately 36 or 40 weeks, depending upon whether the treatment duration was 8 or 12 weeks, respectively.

Number of Subjects (planned and analyzed): 60 subjects planned, 63 subjects were enrolled (intent-to-treat [ITT] population) and received at least 1 dose of study drugs (safety population); assigned to 2 groups:

- Group A: Subjects without cirrhosis (40 subjects enrolled) were randomly assigned in a 1:1 ratio to receive either 8 weeks (Group A1, 20 subjects; 12 were treatment naïve) or 12 weeks (Group A2, 20 subjects; 8 were treatment naïve) of simeprevir 150 mg once daily in combination with sofosbuvir 400 mg once daily therapy.

  Randomization in Group A was stratified by treatment history (treatment naïve or experienced) and METAVIR score (F0 to F2 and F3). There were 2 strata, as shown in the table below: (1) treatment naïve and F0 to F2; and (2) treatment experienced and/or F3.

Group	N	Fibrosis Stage (METAVIR)	PegIFN/RBV Experience	Stratum
A1	20	F0, F1, or F2	Naïve	1
		F0, F1, or F2 F3	Experienced Naïve/Experienced	2
A2	20	F0, F1, or F2	Naïve	1
		F0, F1, or F2 F3	Experienced Naïve/Experienced	2

PegIFN/RBV = pegylated interferon/ribavirin.

- Group B: Subjects with cirrhosis (METAVIR score F4) (23 subjects enrolled; 12 were treatment naïve) were assigned to receive treatment for 12 weeks with simeprevir 150 mg once daily in combination with sofosbuvir 400 mg once daily therapy.

An aim of the study was to enroll at least 50% treatment-naïve subjects. Of the 63 enrolled subjects, 33 (52.4%) were treatment naïve.

Diagnosis and Main Criteria for Inclusion: Men or women between 18 and 70 years of age, inclusive, with HCV genotype 4 infection (confirmed at screening), a screening plasma HCV RNA of >10,000 IU/mL, HCV treatment naïve or experienced (treatment-experienced subjects must have had at least 1 documented previous course of pegylated interferon/ribavirin [PegIFN/RBV] therapy for at least 12 consecutive weeks), and documented absence of cirrhosis based on liver biopsy (specimen length of 15 mm or more) or presence of cirrhosis documented by liver biopsy (specimen length of 15 mm or more) or FibroScan (>14 kPa), were planned to be enrolled. Subjects with cirrhosis must have had a hepatic imaging procedure (ultrasound, computed tomography, or magnetic resonance imaging) within 6 months before Day 1 to exclude hepatocellular carcinoma.

Subjects with hepatic decompensation, with any liver disease other than caused by HCV infection and/or with an HCV infection other than genotype 4, with a hepatitis B or human immunodeficiency virus (HIV) co-infection, or who had a past history of treatment with an approved or investigational direct-acting antiviral agent were excluded.

Test Product, Dose and Mode of Administration, Batch No.: Simeprevir (150 mg capsules) and sofosbuvir (400 mg tablets) were taken orally once daily with food. The lot number for simeprevir was 4370088; the lot numbers for sofosbuvir were 4370087, 4370089, 4370090, and 4370222.

Duration of Treatment: Duration of treatment was either 8 or 12 weeks, depending on the treatment group.

Criteria for Evaluation: Samples for the determination of HCV RNA levels were taken at predefined time points and processed in real time. The percentage of subjects in each group and overall with SVR4, SVR12, SVR24, on-treatment failure (including viral breakthrough), and viral relapse were reported. Complete SVR24 data were not available at the cutoff date for this analysis; the SVR24 results will be reported in the final clinical study report. The percentage of subjects with on-treatment undetectable HCV RNA on Day 7 and at Weeks 2, 4, 8 (EOT for Group A1), and 12 (EOT for Groups A2 and B) was calculated. A pharmacogenomic blood sample was collected at screening to determine the host *IL28B* (interleukin 28B [interferon, lambda 3]) genotype.

Safety and tolerability were evaluated throughout the study. The evaluations of safety and tolerability included monitoring of adverse events (AEs), clinical laboratory tests, vital sign measurements, and physical examination at prespecified time points. All AEs were reported until 4 weeks after EOT; thereafter, only serious adverse events (SAEs) and those AEs that were considered by the investigator to be at least possibly related to study drugs were reported until 24 weeks after the EOT.

Statistical Methods: This report describes the results of the primary analysis, including data for all subjects. The primary analysis was performed after the last subject completed the Follow-up Week 12 visit or discontinued earlier. The cutoff date for this report is 31 August 2015.

Sample Size Determination

This study compared response rates (SVR12) in subjects chronically infected with HCV genotype 4 who were treated with simeprevir + sofosbuvir for 8 or 12 weeks against historical control rates of PegIFN/RBV treatment.

A total of 60 subjects (20 each in Groups A1, A2, and B) with an expected overall response rate of 88% provided >99% power to test for a difference with a historical control rate of 42%, using an alpha level of 0.05.

Secondary comparisons were made for the F0 to F3 population (Groups A1 + A2) and the F4 population (Group B).

A total of 40 subjects (20 each in Groups A1 and A2) with an expected overall response rate of 86%, using an alpha level of 0.05, provided >99% power to test for a difference with a historical control rate of 50%.

A total of 20 subjects (in Group B) with an expected response rate of 88%, using an alpha level of 0.05, provided >99% power to test for a difference with a historical control rate of 25%. No adjustments for multiple comparisons were made.

Primary Endpoint

The primary efficacy parameter was the overall percentage of all subjects with SVR12, defined as HCV RNA less than the lower limit of quantification (LLOQ) 12 weeks after cessation of therapy.

Secondary Endpoints

Secondary efficacy endpoints included:

- The percentage of subjects in each group and overall:
  - with SVR4
  - with SVR12
  - with SVR24 (results not presented in this report)
  - with on-treatment failure, including viral breakthrough
  - with viral relapse
- The percentage of subjects with on-treatment undetectable HCV RNA on Day 7 and at Weeks 2, 4, 8 (EOT for Group A1), and 12 (EOT for Groups A2 and B).

RESULTS:

STUDY POPULATION:

A total of 71 subjects were screened, 63 subjects were enrolled into the study, and 40 subjects were randomized in Group A. All 63 subjects in the ITT population received at least 1 dose of study drugs (simeprevir + sofosbuvir), and all subjects completed treatment with study drugs. At the cutoff date for this analysis, 61 (96.8%) subjects were ongoing in the study, with study completion scheduled to occur at Follow-up Week 24. Two subjects prematurely discontinued the study during the follow-up phase

(1 withdrew consent, and 1 died of encephalopathy and gastrointestinal hemorrhage related to underlying liver disease).

Overall, subject demographics and baseline disease characteristics were well balanced between treatment groups. A total of 54.0% of subjects were male. The median (range) age was 51.0 (24-68) years, with 63.5% of subjects aged >40 to ≤65 years. A total of 33 (52.5%) subjects were treatment naïve. The baseline HCV genotype/subtype, as determined by reverse hybridization performed by the local central laboratory, was reported as other (4, 4C/D, and 4H) in 43 (68.3%) subjects, 4A in 19 (30.2%) subjects, and 4C in 1 (1.6%) subject. The *IL28B* CT subtype was the most common, occurring in 35 (55.6%) subjects, followed by the TT (15 [23.8%] subjects) and CC (13 [20.6%]) subjects.

EFFICACY RESULTS:

All (100.0%) 43 subjects with and without cirrhosis who were treated for 12 weeks achieved SVR12; 15 (75.0%) subjects without cirrhosis who were treated for 8 weeks achieved SVR12. The composite historical SVR12 rate for patients treated with PegIFN/RBV was 50% for those without cirrhosis and 25% for those with cirrhosis.

At Week 2 of treatment, 34 (54.0%) subjects had HCV RNA levels <15 IU/mL, and 19 (30.2%) subjects had confirmed undetectable levels. At Week 4, 59 (93.7%) subjects had HCV RNA levels <15 IU/mL, and 48 (76.2%) subjects had confirmed undetectable levels.

All 5 subjects who did not achieve SVR12 were treatment experienced (ie, prior null responders to PegIFN/RBV therapy) and were randomly assigned to the 8 weeks treatment group (Group A1). Based on serial HCV RNA levels measured during the study, the 5 subjects who did not achieve SVR12 were categorized as experiencing viral relapse, defined as HCV RNA levels < LLOQ undetectable or detectable at EOT but ≥ LLOQ during the follow-up phase. Viral relapse was first detected at Follow-up Week 4 (ie, subjects had HCV RNA levels ≥15 IU/mL and therefore did not achieve SVR4).

SAFETY RESULTS:

The majority of subjects (51 [81.0%]) experienced at least 1 adverse event (AE). The AEs reported in ≥10% of all subjects were lipase increased (14.3%), pruritus (14.3%), headache (12.7%), and hyperbilirubinemia (11.1%). The AEs considered by the investigator to be at least possibly related to one or both of the study drugs and reported in ≥5% of subjects were pruritus (7 [11.1%] subjects), fatigue (5 [7.9%] subjects), and headache (4 [6.3%] subjects).

The majority of AEs were Grade 1 or 2 in severity. Four (6.3%) subjects were reported with any Grade 3 or 4 AE: lipase increased in 3 (4.8%) subjects, and hepatic lesion in 1 (1.6%) subject. No AEs led to premature discontinuation of study drugs.

One death occurred during the follow-up phase of the study. The treatment-naïve subject with cirrhosis died of encephalopathy and gastrointestinal hemorrhage on Day 188, after completing study drugs on Day 84 and achieving SVR12. The investigator considered the causality of death as not related to study drugs but related to HCV infection.

One treatment-naïve subject with cirrhosis experienced the SAEs of pulmonary hypertension and pulmonary effusion during the treatment phase. The SAEs were considered by the investigator as not related to study drugs. No other SAEs were reported during the treatment phase.

A total of 16 (25.4%) subjects were reported with at least 1 AE of interest during the treatment phase, including 9 of 40 subjects without cirrhosis and 7 of 23 subjects with cirrhosis. Ten (30.3%) treatment-naïve and 6 (20.0%) treatment-experienced subjects were reported with at least 1 AE of interest. Adverse events of interest were reported at the following percentages in the total population: pruritus (14.3%), hyperbilirubinemia (11.1%), rash (generalized erythema, 1.6%), dyspnea (3.2%), and neutropenia (1.6%).

All AEs of interest were reported as Grade 1 or 2 in severity, and none led to premature discontinuation of study drugs or the study.

Mean changes from baseline in vital signs parameters were generally small and not considered clinically relevant. Physical examination abnormalities were considered not clinically relevant.

STUDY LIMITATIONS:

No notable study limitations were identified by the sponsor.

CONCLUSIONS:

The combination of simeprevir + sofosbuvir achieved an SVR12 rate of 100% in HCV genotype 4 subjects, with and without cirrhosis and regardless of prior treatment history, who were treated for 12 weeks, and achieved the primary objective of demonstrating superiority in SVR12 rates compared with historical controls. All subjects who achieved SVR4 also achieved SVR12. An SVR12 rate of 75% was observed in subjects without cirrhosis who were treated with simeprevir + sofosbuvir for 8 weeks, and this rate also showed superiority compared with historical controls. All 5 subjects who did not achieve SVR12 were treatment experienced. They had undetectable HCV RNA levels at EOT but did not achieve SVR4 and were therefore categorized as having experienced viral relapse.

An 8-week or 12-week regimen of simeprevir 150 mg once daily, in combination with sofosbuvir 400 mg once daily, was generally safe and well tolerated. One death occurred during the follow-up phase of the study in a treatment-naïve subject with cirrhosis who achieved SVR12. The investigator considered the causality of death as not related to study drugs but related to HCV infection. One treatment-naïve subject with cirrhosis experienced the SAEs of pulmonary hypertension and pulmonary effusion during the treatment phase. The SAEs were considered by the investigator as not related to study drugs. No other SAEs were reported during the treatment phase.

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