FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Multicenter, Randomized, Phase 3, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Velpatasvir ± Ribavirin for 12 Weeks in Subjects with Chronic HCV Infection and Decompensated Cirrhosis
Name of Test Drug:	Sofosbuvir/velpatasvir (SOF/VEL) fixed-dose combination (FDC)
Dose and Formulation:	SOF/VEL FDC (400/100 mg) tablet
Indication:	Hepatitis C virus Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
Study No.:	GS-US-342-4019
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	Not Applicable Not Applicable
ClinicalTrials.gov Identifier:	NCT02996682
Study Start Date:	26 December 2016 (First Subject Screened)
Study End Date:	08 May 2018 (Last Subject Last Observation)
Principal or Coordinating Investigator:	Name: Tetsuo Takehara, MD, PhD Affiliation: PPD
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Report Date:	23 August 2018
Previous Report Date(s):	02 April 2018 (Interim Clinical Study Report [CSR])

STUDY SYNOPSIS

Study GS-US-342-4019
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Multicenter, Randomized, Phase 3, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Velpatasvir ± Ribavirin for 12 Weeks in Subjects with Chronic HCV Infection and Decompensated Cirrhosis

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled across 33 sites in Japan.

Publications: Takehara T, Kurosaki M, Tanaka Y, Tatsumi T, Ikeda F, Takikawa Y, et al. Sofosbuvir/Velpatasvir with or without Ribavirin for 12 Weeks in HCV-Infected Japanese Subjects with Decompensated Cirrhosis [Presentation]. 54th Annual Meeting of Japan Society of Hepatology; 2018 June 15; Osaka, Japan.

Study Period:

26 December 2016 (First Subject Screened)
13 February 2018 (Last Subject Last Observation for the Primary Endpoint)
08 May 2018 (Last Subject Last Observation for this Report)

Phase of Development: Phase 3

Objectives:

The primary objectives of this study were as follows:

- To evaluate the antiviral efficacy of therapy with sofosbuvir/velpatasvir (SOF/VEL) fixed-dose combination (FDC) with or without ribavirin (RBV) for 12 weeks as measured by the proportion of subjects with sustained virologic response 12 weeks after cessation of treatment (SVR12)
- To evaluate the safety and tolerability of each treatment regimen

The secondary objectives of this study were as follows:

- To determine the proportion of subjects who attained SVR at 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure
- To evaluate therapeutic efficacy as measured by the change of Child-Pugh-Turcotte (CPT) score and Model for End-Stage Liver Disease (MELD) score
- To evaluate the kinetics of circulating hepatitis C virus (HCV) RNA during treatment and after cessation of treatment
- To evaluate the emergence of viral resistance to SOF and VEL during treatment and after cessation of treatment

The exploratory objectives of this study were as follows:

- To identify or validate genetic markers that may be predictive of the natural history of disease, response to therapy and/or tolerability of medical therapies through genetic discovery research (e.g., genomics), in subjects who provided their separate and specific consent
- To assess the effect of treatment with SOF/VEL ± RBV on health-related quality of life (HRQOL)

Methodology: This Phase 3, randomized, open-label, multicenter study in Japan assessed the antiviral efficacy, safety, and tolerability of SOF/VEL ± RBV administered for 12 weeks in subjects with chronic HCV infection with decompensated cirrhosis.

Approximately 100 subjects were planned to be randomized (1:1) to 1 of the following 2 treatment groups:

- **SOF/VEL 12 Week group:** SOF/VEL FDC tablet (400/100 mg) once daily for 12 weeks
- **SOF/VEL+RBV 12 Week group:** SOF/VEL FDC tablet (400/100 mg) once daily with RBV capsules for 12 weeks

Randomization was stratified by CPT class at screening (CPT B/CPT C) and HCV genotype (genotype 1/nongenotype 1). Approximately 15 subjects with nongenotype 1 HCV infection were planned to be enrolled. For the purposes of randomization, a subject with non-definitive or mixed HCV genotype results by central laboratory analysis was considered nongenotype 1.

Approximately 10% of subjects may have had CPT class C cirrhosis at screening.

Initially, only subjects with CPT class B cirrhosis (score 7 to 9) at screening were planned to be enrolled. Subjects with CPT class C cirrhosis at screening (score 10 to 12) were planned to be enrolled after the Data Monitoring Committee (DMC) had reviewed the accumulated safety data when the first 20 subjects enrolled had completed 4 weeks of treatment (or early treatment discontinuation) and concluded that these data supported enrollment of subjects with CPT class C cirrhosis.

All subjects were to complete the posttreatment Week 4, 12, and 24 visits regardless of their treatment duration.

Subjects who provided separate and specific consent were eligible for participation in the genomics substudy. A blood sample was drawn for this substudy at the Day 1 visit or at any time during the study.

This final synoptic CSR summarizes the results of the final analysis of data collected throughout the course of the study, after all subjects had completed the posttreatment Week 24 visit or had prematurely discontinued from the study. Analysis of data collected for the primary efficacy endpoint (SVR12) was reported in the interim CSR (02 April 2018).

Number of Subjects (Planned and Analyzed):
Planned: Approximately 100 subjects
Analyzed:

- All Randomized Analysis Set: 102 subjects
- Full Analysis Set (FAS): 102 subjects
- Safety Analysis Set: 102 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males or nonpregnant/nonlactating females ≥ 20 years of age, with chronic HCV infection and decompensated cirrhosis.

Duration of Treatment: Treatment duration was 12 weeks.

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

- **SOF/VEL** was administered orally to subjects at a dose of 400/100 mg (1 FDC tablet daily).
- **RBV** (Rebetol®) was administered orally to subjects with CPT class B cirrhosis using weight-based dosing at a total daily dose of 600, 800, or 1000 mg/day (3, 4, or 5 × 200-mg capsules divided twice daily) and subjects with CPT class C cirrhosis at a total daily dose of 600 mg/day (3 × 200-mg capsules divided twice daily).

The batch numbers of study drugs administered in this study were as follows:

- **SOF/VEL:** DU1508B1
- **RBV:** B001B and B002B

Reference Therapy, Dose, Mode of Administration, and Batch No.: None

Criteria for Evaluation:

Efficacy: Blood samples to determine HCV RNA levels were collected from subjects at screening; Day 1 (predose); Weeks 2, 4, 8, and 12 during treatment; early termination (if applicable); and posttreatment Weeks 4, 12, and 24. The COBAS® AmpliPrep®/ COBAS® TaqMan® HCV Quantitative Test v2.0 was used to quantify HCV RNA in this study. The lower limit of quantitation (LLOQ) of the assay was 15 IU/mL.

Pharmacokinetics: A single pharmacokinetic (PK) blood sample was collected from all subjects at each on treatment visit at Weeks 2, 4, 8, and 12 or early termination and archived for PK analysis of SOF, SOF metabolites GS-566500 and GS-331007, VEL, and RBV (if appropriate).

Safety: Safety assessments included monitoring of adverse events (AEs) and concomitant medications, clinical laboratory analyses, vital signs measurements, and physical examinations.

Quality of Life: The HRQOL questionnaires included the 36-Item Short Form Health Survey (SF-36), Chronic Liver Disease Questionnaire-HCV (CLDQ-HCV), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire, and the Work Productivity and Activity Impairment: Hepatitis C (WPAI: Hep C) questionnaire. These were completed by subjects at Day 1, Week 12 (or at end of treatment, if early discontinuation), and posttreatment Week 12.

Statistical Methods:

Efficacy: The primary efficacy endpoint was the proportion of subjects with SVR12, defined as HCV RNA < LLOQ (ie, < 15 IU/mL) 12 weeks after cessation of treatment, in the FAS. The FAS included all subjects who were randomized into the study and received at least 1 dose of study drug. Point estimates and 2-sided 95% exact confidence intervals (CIs) for SVR12 based on the Clopper-Pearson method were provided for each treatment group {Clopper 1934}. In the primary efficacy analysis, the SVR12 rate for subjects in each of the 2 treatment groups was compared to the spontaneous clearance rate of 1% using a 2-sided exact 1-sample binomial test with Bonferroni alpha adjustment (each at the 0.025 significance level).

Secondary efficacy endpoints included the proportion of subjects with SVR4, SVR24, virologic failure, and HCV RNA < LLOQ while on treatment by study visit; HCV RNA absolute values and changes from baseline through end of treatment (EOT); MELD and CPT score changes from baseline and characterization of HCV drug resistance substitutions at baseline and during and after therapy with SOF/VEL and SOF/VEL+RBV.

Pharmacokinetics: No PK analyses were performed for this report. A population PK analysis of SOF, GS-331007, and VEL are presented in separate population PK reports.

Safety: All subjects who received at least 1 dose of study drug were included in the Safety Analysis Set. Safety assessments included monitoring of AEs, deaths, and concomitant medications, clinical laboratory analyses, body weights, heights, vital signs measurements, and physical examinations. Safety data were analyzed by treatment group and CPT class, and included all data collected on or after the first dose of any study drug up to the date of the last dose of study drug plus 30 days. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.1.

Quality of Life: Health-related quality of life was assessed with the SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C questionnaires. A Wilcoxon signed rank test explored within-treatment group changes from baseline to each of the postbaseline time points, and from EOT to each posttreatment time point. A Wilcoxon rank sum test explored between-treatment group differences in change from baseline to each of the postbaseline time points.

All continuous endpoints were summarized using descriptive statistics (sample size, mean, standard deviation [SD], median, first quartile [Q1], third quartile [Q3], minimum, and maximum). All categorical endpoints were summarized by number and percentage of subjects who met the endpoint definitions.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: A total of 102 subjects were randomized into the study. All 102 randomized subjects received at least 1 dose of study drug and were included in both the Safety Analysis Set and FAS (51 subjects in the SOF/VEL 12 Week group and 51 subjects in the SOF/VEL+RBV 12 Week group) (Table 15.8.1.3.1).

The majority of subjects completed study treatment (98.0%, 100 of 102 subjects) (Table 15.8.1.3.1). Two subjects (2.0%) prematurely discontinued study treatment (both subjects were in the SOF/VEL+RBV 12 Week group), both due to AEs.

No notable differences in demographic or baseline characteristics were observed between the interim analyses and the final analyses (Table 15.8.3.1.1 and Listings 16.2.4.1 and 16.2.4.2.1).

Efficacy Results:

Analysis of the primary efficacy endpoint is reported in Section 9 of the interim CSR (02 April 2018).

The study met the primary efficacy endpoint of an SVR12 rate that was statistically superior compared with the spontaneous clearance rate of 1% ($p < 0.001$) in both treatment groups.

The SVR12 rates were as follows:

- SOF/VEL 12 Week group: 92.2% (47 of 51 subjects; 95% CI: 81.1% to 97.8%)
- SOF/VEL+RBV 12 Week group: 92.2% (47 of 51 subjects; 95% CI: 81.1% to 97.8%)

A comparison of the results for SVR12 and SVR24, a secondary efficacy endpoint, is presented in the table below. No subjects relapsed between posttreatment Weeks 12 and 24 (Listing 16.2.6.4). The SVR12 rates reported in the interim analysis were maintained in the SVR24 analysis, with a 100% concordance between SVR12 and SVR24 (Table 15.9.2.3).

	SOF/VEL 12 Weeks (N = 51)	**SOF/VEL+RBV 12 Weeks (N = 51)**
SVR12	47/51 (92.2%)	47/51 (92.2%)
95% CI	81.1% to 97.8%	81.1% to 97.8%
SVR24	47/51 (92.2%)	47/51 (92.2%)
95% CI	81.1% to 97.8%	81.1% to 97.8%
Concordance	100%	100%

HCV RNA was analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with limit of quantitation 15 IU/mL.
SVRx is sustained virologic response (HCV RNA < LLOQ) x weeks after stopping study treatment.
A missing SVR value was imputed as a success if it was bracketed by values that were termed successes (ie, '< LLOQ TND' or '< LLOQ detected'); otherwise, the missing SVR value was imputed as a failure. TND = target not detected.
The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.
Only subjects that had both Posttreatment Week 12 and Posttreatment Week 24 data were included in the concordance analysis.
Source: Tables 15.9.2.2 and 15.9.2.3

Among the 94 subjects who achieved SVR24, 37.2% (35 of 94) improved CPT class and 3.2% (3 of 94) worsened CPT class from baseline to posttreatment Week 24 (Table 15.9.4.1).

	Overall (N=94) Baseline CPT Class		
	CPT A [5-6] (N=3)	**CPT B [7-9] (N=76)**	**CPT C [10-15] (N=15)**
Posttreatment Week 24 CPT Class			
CPT A [5-6]	3/3 (100.0%)	26/75 (34.7%)	0/15
CPT B [7-9]	0/3	46/75 (61.3%)	9/15 (60.0%)
CPT C [10-15]	0/3	3/75 (4.0%)	6/15 (40.0%)
No Assessment	0	1	0

CPT score was calculated using prothrombin activation % for the coagulation parameter.
Baseline value was the last available value on or prior to first dose date of any study drug.
Source: Table 15.9.4.1

Virologic Resistance Results: Full details on the resistance analysis were reported in Section 9.3.1 of the interim CSR (02 April 2018). No additional resistance analyses were performed since no subjects relapsed after posttreatment Week 12.

Pharmacokinetics Results: No PK analyses were performed for this report.

Safety Results: All AEs and laboratory abnormalities discussed in this CSR were treatment emergent and are referred to as AEs and laboratory abnormalities in this report, unless otherwise specified. Evaluations of safety data through 30 days after the last dose of study drugs were summarized in Section 11 of the interim CSR (02 April 2018).

Adverse Events and Serious Adverse Events

A small number of minor updates were made to previously reported AE data due to the ongoing nature of the study and data reconciliation. One additional Grade 1 AE of portal hypertensive gastropathy was reported in a subject in the SOF/VEL group (Subject PPD) (Listing 16.2.7.7). The AE had an onset of Day 76 and was unresolved at the time of database finalization. It was not considered related to study drug by the investigator. A previously reported nontreatment-emergent SAE of sudden hearing loss in a subject in the SOF/VEL+RBV group (Subject PPD) was updated to acoustic neuroma. Medication and other treatment were required in addition to a previously reported hospitalization.

No additional treatment-emergent Grade 3 or 4 AEs, AEs that led to study drug discontinuation, serious adverse events (SAEs), or deaths were reported (Listing 16.2.7.7). One additional nontreatment-emergent SAE of hepatic encephalopathy was reported on posttreatment Day 112 in a subject in the SOF/VEL+RBV group (Subject PPD) (Listing 16.2.7.7). It was not considered related to study drug by the investigator.

These changes did not impact the overall interpretation or conclusions of the safety profile of SOF/VEL or SOF/VEL+RBV in this study, as described in the interim CSR (02 April 2018).

All AE results are provided in Tables 15.11.2.1.1.1 to 15.11.5.8 and Listings 16.2.7.1 to 16.2.7.6.

Clinical Laboratory Results

No updates were made to previously reported laboratory abnormalities.

All laboratory results are provided in Tables 15.11.6.1.1 to 15.11.6.3 and Listings 16.2.8.1.1 to 16.2.8.2.1.

Vital Sign Measurements and ECGs

No notable changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure, or pulse) were observed during the study.

All vital sign and ECG results and other safety-related results are provided in Tables 15.11.7.1 to 15.11.8.3 and Listings 16.2.8.2.1 to 16.2.8.2.3.2.

Quality of Life Results: Complete details on the HRQOL questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C) through posttreatment Week 12 are reported in Section 12 of the interim CSR (02 April 2018). Subjects did not complete questionnaires at posttreatment Week 24, so no further analyses were conducted.

CONCLUSIONS: The conclusions from this final analysis of Study GS-US-342-4019 in Japanese subjects with chronic HCV infection and decompensated cirrhosis are as follows:

- Both treatment groups met the study primary efficacy endpoint with SVR12 rates being statistically superior to the spontaneous clearance rate of 1% ($p < 0.001$).
  - The SVR12 rate in the SOF/VEL 12 Week group was 92.2%.
  - The SVR12 rate in the SOF/VEL+RBV 12 Week group 92.2%.
- The overall concordance between SVR12 and SVR24 was 100.0%. No subjects relapsed between posttreatment Weeks 12 and 24.
- Treatment with SOF/VEL or SOF/VEL+RBV for 12 weeks was generally safe and well tolerated. In this population of subjects with advanced liver disease, the addition of RBV to SOF/VEL was associated with increased toxicity.