FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 Weeks in Subjects with Chronic HCV
Name of Test Drug:	Sofosbuvir (SOF)/velpatasvir (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-342-1518
Phase of Development:	Phase 3
IND No.:	Not Applicable
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	NCT02671500
Study Start Date:	19 April 2016 (First Subject Screened)
Study End Date:	05 January 2018 (Last Subject Last Observation for the Primary Endpoint) 27 March 2018 (Last Subject Last Observation for this Report)
Principal or Coordinating Investigator:	Name: Lai Wei, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Luisa Stamm, MD, PhD Telephone: PPD Fax: PPD
Report Date:	16 July 2018
Previous Report Date:	06 March 2018

STUDY SYNOPSIS

Study GS-US-342-1518
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 Weeks in Subjects with Chronic HCV

Investigators: This was a multicenter study.

Study Centers: 38 sites (25 in China, 2 in Malaysia, 2 in Singapore, 5 in Thailand, and 4 in Vietnam)

Publications:

Lim SG, Rosmawati M, Phuong L, Hoi PT, McNabb BL, Lu S, et al. Safety and Efficacy of Sofosbuvir/Velpatasvir in a Genotype 1-6 HCV Infected Population from Singapore, Malaysia, Thailand, and Vietnam: Results from a Phase 3, Clinical Trial [Abstract 1094]. Hepatology 2017; 66 (1 Suppl): 586A.

Study Period:

19 April 2016 (First Subject Screened)
05 January 2018 (Last Subject Last Observation for the Primary Endpoint)
27 March 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 efficacy of treatment with sofosbuvir (SOF)/velpatasvir (VEL; GS-5816) for 12 weeks in subjects with chronic hepatitis C virus (HCV) infection as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after discontinuation of study drug (SVR12)
- To evaluate the safety and tolerability of treatment with SOF/VEL for 12 weeks

The secondary objectives of this study were as follows:

- To determine the proportion of subjects with SVR at 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure
- To evaluate the kinetics of circulating 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:

- 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 (eg, pharmacogenomics), in subjects who provide their separate and specific consent
- To assess the effect of treatment on health related quality of life (QoL)

Methodology: This Phase 3, open-label, multicenter, international study evaluated the antiviral efficacy, safety, and tolerability of SOF/VEL for 12 weeks in treatment-naive and treatment-experienced subjects with chronic HCV infection, with or without cirrhosis, in China (Region 1), and Malaysia, Singapore, Thailand, and Vietnam (collectively referred to as Region 2).

Approximately 360 subjects total were planned for enrollment. The table below presents the number of subjects by region and HCV genotype planned to be enrolled. Approximately 20% of enrolled subjects may have been treatment experienced and approximately 20% of enrolled subjects may have had compensated cirrhosis.

All enrolled subjects were to receive SOF/VEL fixed-dose combination (FDC) (400/100 mg) once daily for 12 weeks.

HCV Genotype	Genotype 1	Genotype 2	Genotype 3	Genotypes 4, 5, 6	Total
Region 1 (China)	80	60	60	60	260
Region 2 (Malaysia, Singapore, Thailand, Vietnam)	100				100

All subjects were to complete the posttreatment Week 4 visit, regardless of their treatment duration. All subjects who achieved SVR4, defined as HCV RNA less than the lower limit of quantitation (< LLOQ) at posttreatment Week 4, were to complete the posttreatment Week 12 visit. All subjects who achieved SVR12, defined as HCV RNA < LLOQ at posttreatment Week 12, were to complete the posttreatment Week 24 visit. This clinical study report (CSR) reports efficacy and safety data for subjects in Region 1, Region 2, and overall (Regions 1 and 2 combined).

The First Interim CSR (06 March 2018) presented all data collected through the posttreatment Week 12 visit. This Final CSR presents the final results through posttreatment Week 24. These analyses were conducted when all subjects had completed the posttreatment Week 24 visit or had prematurely discontinued from the study. All data collected by the data finalization date (07 May 2018) were included in these analyses.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 360 subjects overall

- Approximately 260 subjects from Region 1 (China)
- Approximately 100 subjects from Region 2 (Malaysia, Singapore, Thailand, Vietnam)

Analyzed:

- All Enrolled Analysis Set, Full Analysis Set (FAS), and Safety Analysis Set: 375 subjects overall
- 264 subjects from Region 1 (China)
- 111 subjects from Region 2 (Malaysia, Singapore, Thailand, Vietnam)

Diagnosis and Main Criteria for Inclusion: Eligible subjects were male or nonlactating/nonpregnant females aged 18 years of age or older, with chronic genotypes 1, 2, 3, 4, 5, 6, or indeterminate HCV infection, who were treatment naive or treatment experienced; and had documentation of the presence or absence of cirrhosis.

Duration of Treatment: 12 weeks of treatment and up to 24 weeks of posttreatment follow-up

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

SOF/VEL FDC 400/100 mg was administered orally once daily without regard to food.

The batch numbers of SOF/VEL administered in this study were 16SXG007U for Region 1 and DU1506B1 for Region 2.

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

Criteria for Evaluation:

Efficacy: Blood samples to determine serum HCV RNA levels were collected from subjects at screening, baseline/Day 1 (predose), Weeks 1, 2, 4, 6, 8, 10, and 12 during treatment, at early termination (if applicable); and posttreatment Weeks 4, 12 (if applicable), and 24 (if applicable). The COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to quantify HCV RNA. The LLOQ of the assay is 15 IU/mL.

Virology: Baseline deep sequencing analysis of HCV nonstructural protein (NS)5A and/or NS5B coding regions was performed for all subjects. For all subjects with virologic failure, deep sequencing was performed at the first time point after virologic failure if the plasma/serum sample was available and HCV RNA was > 1000 IU/mL. All virologic resistance data are reported at a 15% assay cutoff.

Pharmacokinetics/Pharmacodynamics: No PK/PD assessments were performed for this study.

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

Quality of Life: Health-related quality of life (QoL) was assessed with the Short Form-36 Health Survey (SF-36), which subjects completed at baseline/Day 1; Week 12 (or early termination); and posttreatment Weeks 4 and 12.

Statistical Methods:

Efficacy: Efficacy data were analyzed by region for the analysis of the primary endpoint and by region and genotype for all other analyses.

The primary efficacy endpoint was SVR12 (defined as HCV RNA < LLOQ 12 weeks after discontinuation of study drug) for subjects in the FAS. Details of the statistical methods for the primary endpoint are provided in the First Interim CSR.

Secondary efficacy endpoints included SVR4, SVR24, proportion of subjects with HCV RNA < LLOQ while on treatment by study visit, HCV RNA absolute values and changes from baseline through end of treatment, virologic outcomes (SVR12, on-treatment virologic failure, relapse, and "Other"), and characterization of baseline and emergent HCV drug resistance-associated variants.

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. Results for all secondary efficacy endpoints except SVR24 were presented in the First Interim CSR.

Pharmacokinetics/Pharmacodynamics: No PK/PD assessments were performed for this study.

Safety: All enrolled subjects who received at least 1 dose of study drug were included in the Safety Analysis Set. The primary safety endpoint was any AE leading to permanent discontinuation of study drug. Safety data were summarized by region 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: Details of the statistical methods for QoL are presented in the First Interim CSR.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

A total of 375 subjects (264 in China; 111 subjects in Malaysia, Singapore, Thailand, and Vietnam) were enrolled and received treatment in this study and were included in the FAS and Safety Analysis Set. Of these, 374 subjects (99.7%) completed study treatment. Full details on subject disposition, demographics, and baseline disease characteristics through posttreatment Week 12 were reported in Section 8.3 of the First Interim CSR. Subject disposition for Region 1, Region 2, and overall (Regions 1 and 2 combined) at posttreatment Week 24 is summarized in Table 15.8.1.2. No subjects prematurely discontinued the study between the posttreatment Week 12 and Week 24 visits.

No notable differences in demographic or baseline disease characteristics were observed between the interim analysis and the final analysis. Analyses related to disposition, demographics, baseline disease characteristics, study drug adherence, and exposure are presented in Tables 15.8.1.2, 15.8.3, 15.8.4, and 15.11.1, Figure 15.8.1, and Listings 16.2.1.1, 16.2.1.2, 16.2.4.1, 16.2.4.2.1, 16.2.4.2.2, 16.2.5.1, and 16.2.5.2.

For this Final CSR, an updated important protocol deviation log is provided in Appendix 16.2.2 (Important Protocol Deviation Log).

The following discrepancies were noted following database finalization (data on file) and are not reflected in the respective tables and listings:

- Subject PPD had an ongoing medical history of chronic nephrosis and received concomitant valsartan
- Subject PPD received concomitant paracetamol (not sumatriptan)

Efficacy Results:

Primary Endpoint:

The study met its predefined primary efficacy endpoint: SOF/VEL for 12 weeks resulted in an SVR12 rate of 96.2% (95% CI: 93.1% to 98.2%) in Region 1 (China), which was statistically superior relative to the prespecified performance goal of 85% ($p < 0.001$). In Region 2 (Malaysia, Singapore, Thailand, and Vietnam), treatment with SOF/VEL for 12 weeks resulted in an SVR12 rate of 97.3% (95% CI: 92.3% to 99.4%). Overall (Regions 1 and 2 combined), the SVR12 rate was 96.5% (95% CI: 94.1% to 98.1%).

The results of the primary efficacy analysis presented in this Final CSR are the same as the results presented in the First Interim CSR.

- Virologic Outcomes:

A total of 12 subjects (9 subjects in China; 3 subjects in Region 2 [Malaysia, Singapore, Thailand, and Vietnam]) had virologic failure, all of whom relapsed: 10 subjects with genotype 3b, 1 with genotype 3a, and 1 with genotype 6f infection. One additional subject in China did not achieve SVR12 (lost to follow up). No changes in virologic outcomes occurred between the posttreatment Weeks 12 and 24.

Comparison of SVR4, SVR12, and SVR24:

The proportion of subjects with SVR4, SVR12, and SVR24 is presented in the table below. The SVR rates reported in the First Interim CSR were maintained in this Final CSR, with no additional relapses. The SVR24 rate was the same as the SVR12 rate.

	Region 1 (China) (N = 264)	Region 2 (Malaysia, Singapore, Thailand, Vietnam) (N = 111)	Overall (Regions 1 and 2) (N = 375)
SVR4	254/264 (96.2%)	110/111 (99.1%)	364/375 (97.1%)
95% CI	93.1% to 98.2%	95.1% to 100.0%	94.8% to 98.5%
SVR12	254/264 (96.2%)	108/111 (97.3%)	362/375 (96.5%)
95% CI	93.1% to 98.2%	92.3% to 99.4%	94.1% to 98.1%
SVR24	254/264 (96.2%)	108/111 (97.3%)	362/375 (96.5%)
95% CI	93.1% to 98.2%	92.3% to 99.4%	94.1% to 98.1%

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 is imputed as a success if it is bracketed by values that are termed successes (ie, '< LLOQ TND' or '< LLOQ detected'); otherwise, the missing SVR value is imputed as a failure. TND = target not detected.
The exact 95% CI for the proportion is based on the Clopper-Pearson method.
Source: Table 15.9.2.2

Concordance between SVR12 and SVR24:

A total of 361 subjects treated with SOF/VEL for 12 weeks had HCV RNA assessed at both posttreatment Weeks 12 and 24, with 100% concordance between SVR12 and SVR24.

	Region 1 (China)		Region 2 (Malaysia, Singapore, Thailand, Vietnam)		Overall (Regions 1 and 2)	
	Yes (N = 253)	No (N = 0)	Yes (N = 108)	No (N = 0)	Yes (N = 361)	No (N = 0)
SVR12						
Yes	253	0	108	0	361	0
No	0	0	0	0	0	0
Positive predictive value	100%		100%		100%	

HCV RNA was analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with limit of quantitation 15 IU/mL.
Only subjects who have both Posttreatment Week 12 and Posttreatment Week 24 data were included in the analysis.

All efficacy analyses are provided in Tables 15.9.1 through 15.9.4.1, Figures 15.9.1 through 15.9.2.5.4, and Listings 16.2.6.1 through 16.2.6.4.

- Virologic Resistance:

Full details on the resistance analysis are reported in Section 9.3.2 of the First Interim CSR. No additional resistance analyses were performed because no subjects relapsed between posttreatment Week 12 and posttreatment Week 24.

Pharmacokinetics/Pharmacodynamics Results: No PK/PD assessments were performed for this study.

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. Evaluation of safety through 30 days after the last dose of study drugs through posttreatment Week 12 was summarized in Section 11 of the First Interim CSR. Changes in safety results relative to posttreatment Week 12 (First Interim CSR) for Region 1, Region 2, and overall (Regions 1 and 2 combined) are summarized in this Final CSR.

A small number of updates were made to previously reported AE data due to the ongoing nature of the study and data reconciliation. These changes were primarily associated with minor clarifications to AE details and newly reported Grade 1 or 2 AEs (Listing 16.2.7.7). These changes did not impact the overall interpretation of data or conclusions of this study. Listing 16.2.7.7 provides a detailed listing of any newly reported AEs and AEs with changes other than resolution date between the First Interim CSR and this Final CSR. All AE results are provided in Tables 15.11.3.1.1 through 15.11.6.1, and Listings 16.2.7.1 through 16.2.7.7. The following AE was not reported prior to database finalization and is not reflected in the AE tables and listings: Subject PPD had a non-serious AE of Grade 1 increased creatine kinase at the Week 4 visit that was considered not related to study drug (data on file).

No new subject pregnancies, treatment-emergent SAEs, treatment-emergent Grade 3 or 4 AEs, or AEs that led to study drug discontinuation were reported for this Final CSR (Listings 16.2.7.2, 16.2.7.4, 16.2.7.5, 16.2.7.7, and 16.2.8.3). Two additional nontreatment-emergent SAEs in 2 subjects (both in China) were reported, neither of which was considered related to study drug: a Grade 3 event of fibroadenoma of breast on posttreatment Day 155 (resolved on posttreatment Day 159) and a Grade 3 event of foot fracture on posttreatment Day 120 (resolved on posttreatment Day 165; Listing 16.2.7.7).

Clinical laboratory assessments and ECGs were not performed at the posttreatment Week 24 visit; therefore, there were no changes to the clinical laboratory results or ECG results reported in the First Interim CSR. All laboratory results are provided in Tables 15.11.6.1.1 through 15.11.6.3, Figures 15.11.6.1 through 15.11.6.10, and Listings 16.2.8.1.1 through 16.2.8.1.9. All ECG results are provided in Table 15.11.9, and Listings 16.2.8.2.3.1 and 16.2.8.2.3.2. The following ECG abnormality was not reported prior to database finalization and is not reflected in the ECG listings: Subject PPD had an abnormal U wave at the Week 1 visit, which the investigator considered not clinically significant (data on file).

Vital sign measurements (diastolic and systolic blood pressure, pulse, respiratory rate, and temperature) and weight were collected at the posttreatment Week 24 visit. No notable changes relative to posttreatment Week 12 (First Interim CSR) were observed. All vital sign, height, and weight measurements are provided in Tables 15.11.7.1 through 15.11.7.3, and Listings 16.2.8.2.1 and 16.2.8.2.2.

Other Results: The health-related QoL survey was not completed by subjects at the posttreatment Week 24 visit. Details on QoL results are presented in the First Interim CSR.

CONCLUSIONS:

The conclusions from the interim and final analyses of Study GS-US-342-1518 are as follows:

- Overall, treatment with SOF/VEL for 12 weeks resulted in a high SVR12 rate of 96.5% (95% CI: 94.1% to 98.1%).
- In Region 1 (China), the study met its predefined primary efficacy endpoint: treatment with SOF/VEL for 12 weeks resulted in an SVR12 rate of 96.2% (95% CI: 93.1% to 98.2%), which was statistically superior relative to the prespecified performance goal of 85% ($p < 0.001$).
- In Region 2 (Malaysia, Singapore, Thailand, Vietnam), treatment with SOF/VEL for 12 weeks resulted in a high SVR12 rate of 97.3% (95% CI: 92.3% to 99.4%).
- Treatment with SOF/VEL for 12 weeks was generally well tolerated. There were no treatment-emergent Grade 3 or 4 AEs, a low incidence of SAEs, no discontinuations due to AEs, no deaths, and no clinically meaningful laboratory abnormalities.