FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3, Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 Weeks with Sofosbuvir and Ribavirin for 12 Weeks in Subjects with Chronic Genotype 2 HCV Infection
Name of Test Drug:	Sofosbuvir (SOF)/velpatasvir (VEL, GS-5816) Fixed-Dose Combination (FDC)
Dose and Formulation:	Sofosbuvir/velpatasvir 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-342-1139 (ASTRAL-2)
Phase of Development:	Phase 3
IND No.:	118605
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	NCT02220998
Study Start Date:	22 September 2014 (First Subject Screened)
Study End Date:	03 September 2015 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Mark Sulkowski, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Anu Osinusi, MD Telephone: PPD Fax: PPD
Report Date:	25 January 2016
Previous Report Date(s):	11 August 2015 (Interim Clinical Study Report)

STUDY SYNOPSIS

Study GS-US-342-1139
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3, Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 Weeks with Sofosbuvir and Ribavirin for 12 Weeks in Subjects with Chronic Genotype 2 HCV Infection

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled across 51 sites in the United States (US).

Publications: Asselah T, Charlton M, Feld J, Foster GR, Mcnally J, Brainard DM, et al. The ASTRAL Studies: Evaluation of SOF/GS-5816 Single Tablet Regimen for the Treatment of Genotype 1-6 HCV Infection [Poster P1332]. J Hepatol 2015;62:S855-S6.

Sulkowski, MS., Brau N., Lawitz E., Shiffman ML, Towner WL, Ruane PJ et al. A Randomized Controlled Trial of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 Weeks Compared to Sofosbuvir with Ribavirin for 12 Weeks in Genotype 2 HCV Infected Patients: The Phase 3 ASTRAL-2 Study [Oral 205] Hepatology 2015; 62: 1 (SUPPL) 313A.

Foster GR, Afdhal N, Roberts SK, Brau N, Gane EJ, Pianko S, et al. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. The N Engl J Med 2015;373:2608-2617.

Study Period:

22 September 2014 (First Subject Screened)
03 September 2015 (Last Subject Observation)
09 July 2015 (Last Subject Observation for the Primary Endpoint)

Phase of Development: Phase 3

Objectives:

The primary objectives of this study were as follows:

- To compare the efficacy of treatment with sofosbuvir (SOF)/velpatasvir (VEL, GS-5816) for 12 weeks with that of SOF + ribavirin (RBV) for 12 weeks as measured by the proportion of subjects with sustained virologic response (SVR) 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 each treatment regimen (SVR4 and SVR24)

- To evaluate the proportion of subjects with virologic failure
- To evaluate the kinetics of circulating hepatitis C virus (HCV) RNA during treatment and after cessation of each treatment regimen
- 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 (eg, pharmacogenomics), in subjects who provided their separate and specific consent
- To assess the effect of treatment on health-related quality of life

Methodology: This Phase 3, randomized, open-label, multicenter study assessed the antiviral efficacy, safety, and tolerability of 12 weeks of SOF/VEL treatment compared with 12 weeks of SOF+RBV treatment in subjects with chronic genotype 2 HCV infection.

Approximately 240 subjects were randomized (1:1) to 1 of the following 2 treatment groups:

- **SOF/VEL 12 Week group (Group 1):** SOF/VEL fixed-dose combination (FDC; 400/100 mg) tablet once daily for 12 weeks
- **SOF+RBV 12 Week group (Group 2):** SOF (400 mg) tablet once daily + RBV (1000 or 1200 mg/day divided twice daily) tablets for 12 weeks

Randomization was stratified by the presence or absence of cirrhosis at screening and prior treatment experience (treatment naive versus [vs] treatment experienced). Approximately 20% of subjects may have been treatment experienced and approximately 20% of subjects may have had cirrhosis.

All subjects were to complete the posttreatment Week 4 and 12 visits regardless of their treatment duration. Subjects who had HCV RNA less than the lower limit of quantitation (LLOQ) at the posttreatment Week 12 visit were also to complete the posttreatment Week 24 visit unless a confirmed viral relapse occurred.

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

After completing all required study visits, subjects in the SOF/VEL 12 Week group could enroll into an SVR Registry Study if SVR was achieved or into the Sequence Registry Study if SVR was not achieved.

This final synoptic clinical study report (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 also reported in the interim CSR (11 August 2015).

Number of Subjects (Planned and Analyzed):
Planned: Approximately 240 subjects
Analyzed:

- All Randomized Analysis Set: 269 subjects
- Full Analysis Set: 266 subjects
- Safety Analysis Set: 266 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males or nonpregnant/nonlactating females of ≥ 18 years of age, with chronic genotype 2 HCV infection, were HCV treatment naive or treatment experienced, and had documentation of the presence or absence of cirrhosis.

Duration of Treatment: Treatment duration was 12 weeks, with up to 24 weeks of posttreatment follow-up.

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

- **SOF/VEL** FDC tablets were administered orally to subjects in the SOF/VEL 12 Week group at a dose of 400/100 mg (1 FDC tablet once daily).

The batch number of SOF/VEL administered in this study was DU1403B1.

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

- **SOF** was administered orally to subjects in the SOF+RBV 12 Week group at a dose of 400 mg (1 × 400-mg tablet once daily).
- **RBV** was administered orally to subjects in the SOF+RBV 12 Week group at a total daily dose of 1000 or 1200 mg/day (5 or 6 × 200-mg tablets divided twice daily).

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

- **SOF**: 14SB006UA
- **RBV**: AB7658Z

Criteria for Evaluation:

Efficacy: This final synoptic CSR provides analyses of the primary efficacy endpoint, SVR12, and HCV RNA levels at posttreatment Week 24. Efficacy analyses at all other scheduled assessment time points were described in the interim CSR (11 August 2015). The COBAS® AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to quantify HCV RNA in this study. The LLOQ of the assay was 15 IU/mL.

Pharmacokinetics: The interim CSR (11 August 2015) describes details on the collection of blood samples to determine plasma concentrations of SOF, its metabolites GS-566500 and GS-331007, VEL, and RBV (if appropriate). No pharmacokinetic (PK) analyses were performed for this report.

Safety: The interim CSR (11 August 2015) provides analyses of adverse events (AEs) and concomitant medications, clinical laboratory analyses, vital sign measurements, electrocardiograms (ECGs), and physical examinations. This final synoptic CSR summarizes any new treatment-emergent AEs or changes to previously reported AEs between the data cuts for the interim CSR and the final CSR. Additionally, all serious adverse events (SAEs) collected after the data cutoff for the interim CSR to the end of the study (posttreatment Week 24) are summarized. Serious adverse events occurring > 30 days after the last dose of study drug were considered nontreatment emergent.

Quality of Life: The interim CSR (11 August 2015) provided analyses of the quality of life questionnaires (Short Form Health Survey [SF-36], Chronic Liver Disease Questionnaire [CLDQ]-HCV, Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-F], and Work Productivity and Activity Impairment [WPAI]: Hepatitis C) to assess the effect of treatment on health-related quality of life. This final CSR summarizes additional data at posttreatment Weeks 12 and 24 and any changes to data that were previously reported in the interim between the data cut offs for the interim CSR and the final CSR.

Statistical Methods:

All tables, figures, and listings produced for this study are provided in Section 15.1 and Appendix 16.2. Documentation of statistical methods is provided in Appendix 16.1.9 of this report and described in detail in Section 7.7 of the interim CSR (11 August 2015).

Efficacy: The primary efficacy endpoint was the proportion of subjects with HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs (SVR12) for the Full Analysis Set. Point estimates and 2-sided 95% exact CIs for SVR12 based on the Clopper-Pearson method were provided for each treatment group. In the primary efficacy analysis, a closed testing procedure was used whereby the noninferiority of SOF/VEL for 12 weeks to SOF+RBV for 12 weeks was tested first. Noninferiority was demonstrated if the lower bound of the 2-sided 95% CI for the difference in SVR12 was greater than −10%. If the lower bound of the CI was greater than −10% (ie, the null hypothesis for noninferiority was rejected), then a 2-sided stratified Cochran-Mantel-Haenszel (CMH) test was used to test for the superiority of SOF/VEL for 12 weeks over SOF+RBV for 12 weeks at a significance level of 0.05.

Secondary efficacy endpoints included SVR4, SVR24, proportion of subjects with HCV RNA < LLOQ by study visit, HCV RNA absolute values and changes from baseline through end of treatment (EOT), and proportion of subjects with virologic failure.

All continuous endpoints were summarized using descriptive statistics (sample size, mean, SD, median, first quartile [Q1], third quartile [Q3], minimum, and maximum) by treatment group and stratification within group (as appropriate). All categorical endpoints were summarized by number and percentage of subjects who met the endpoint definition.

SVR24 rates were calculated using the same method as described for SVR12. If a subject achieved SVR12 and had no further HCV RNA measurement, the subject was counted as a success for SVR24 due to the high correlation between these 2 endpoints {Chen et al 2013}. In addition, an analysis to assess the concordance of SVR12 with SVR24 was performed for subjects with an observed HCV RNA within both the posttreatment Week 12 and posttreatment Week 24 analysis windows.

Pharmacokinetics: No PK analyses were performed for this report.

Safety: All randomized subjects who received at least 1 dose of study drug were included in the Safety Analysis Set. Safety assessments included monitoring of AEs and concomitant medications, clinical laboratory analyses, vital signs measurements, ECGs, and physical examinations. Safety data were analyzed by treatment group 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 18.0.

Quality of Life: The health-related quality of life questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hepatitis C) were completed at baseline/Day 1, Weeks 4, 8, and 12, EOT, early termination (if applicable), and posttreatment Weeks 4, 12, and 24 (if applicable). A Wilcoxon signed rank test explored within-treatment group changes from baseline to each of the 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 time points.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

A total of 266 randomized subjects received treatment in this study and were included in the Full Analysis Set and Safety Analysis Set (Table 15.8.1.3). Full details on subject disposition, demographics, and baseline disease characteristics are reported in Section 8 of the interim CSR (11 August 2015), and subject disposition at posttreatment Week 24 is summarized in Table 15.8.1.3.

No notable differences in demographic or baseline disease characteristics were observed between the interim analyses and the final analyses (Table 15.8.3.1, and Listings 16.2.4.1 and 16.2.4.2.1). There were a small number of additions and changes to concomitant medications that did not change the interpretation of the study results (Table 15.11.7.4 and Listing 16.2.4.4). Analyses related to disposition, demographics, and exposure are presented in Tables 15.8.1.1 to 15.8.4, and 15.11.1, and Figure 15.8.1, and Listings 16.1.7 to 16.2.5.2. In addition, an updated Important Protocol Deviations Log for the study is provided in Appendix 16.2.2.

Efficacy Results:

Primary Endpoint:

The SOF/VEL 12 Week group met the primary endpoint of an SVR12 rate that was noninferior to the SVR12 rate in the SOF+RBV 12 Week group. The SVR12 rates were as follows (Table 15.9.1):

- SOF/VEL 12 Week group: 99.3% (95% CI: 95.9% to 100.0%) of subjects (133 of 134) achieved SVR12
- SOF+RBV 12 Week group: 93.9% (95% CI: 88.4% to 97.3% of subjects (124 of 132) achieved SVR12

The strata-adjusted difference (95% CI) in the proportions was 5.2% (0.2% to 10.3%). Since the lower bound of the 2-sided 95% CI for the difference between groups was greater than the prespecified noninferiority margin of −10%, the efficacy of SOF/VEL for 12 weeks was

demonstrated to be statistically noninferior to SOF+RBV for 12 weeks. There was sufficient evidence to demonstrate the statistical superiority of treatment with SOF/VEL for 12 weeks over SOF+RBV for 12 weeks for SVR12 (p = 0.018; CMH test stratified by cirrhosis status and prior treatment experience). The results of the primary efficacy analysis presented in this report are the same as the results presented in the interim report.

Virologic Outcomes:

Nine of 266 subjects (3.4%) did not achieve SVR12 or SVR24: 1 subject in the SOF/VEL group discontinued study treatment on Day 1 due to AEs, and 8 subjects in the SOF + RBV group either relapsed (6 subjects) or were lost to follow-up (2 subjects) as reported in Section 9 of the interim CSR (11 August 2015). There were no on-treatment virologic failures.

All relapses occurred in the SOF+RBV group. Four subjects relapsed prior to posttreatment Week 4, and 2 subjects relapsed between posttreatment Weeks 4 and 12 (Listing 16.2.6.2). No subjects in either treatment group relapsed between posttreatment Weeks 12 and 24 (Table 15.9.2.3, and Listings 16.2.6.1 and 16.2.6.4).

No changes in virologic outcomes occurred between the Week 12 and 24 visits. The low number of virologic failures in the study precluded meaningful subgroup analysis of SVR.

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 interim analysis were maintained in the SVR24 analysis with no additional relapses. The SVR12 and SVR24 rates were the same for both treatment groups (Tables 15.9.1, 15.9.2.2, and Listing 16.2.6.1).

	SOF/VEL 12 Weeks (N=134)	**SOF+RBV 12 Weeks (N=132)**
SVR4	133/134 (99.3%)	127/132 (96.2%)
95% CI	95.9% to 100.0%	91.4% to 98.8%
SVR12	133/134 (99.3%)	124/132 (93.9%)
95% CI	95.9% to 100.0%	88.4% to 97.3%
SVR24	133/134 (99.3%)	124/132 (93.9%)
95% CI	95.9% to 100.0%	88.4% to 97.3%

HCV RNA was analyzed using the COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with an LLOQ of 15 IU/mL.
SVRx was 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');
A missing SVR24 was imputed as a success if SVR12 was a success; otherwise, the missing SVR value was imputed as a failure.
The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.
Source: Table 15.9.2.2

Concordance between SVR12 and SVR24:

Among subjects in the SOF/VEL 12 Week group, 127 had HCV RNA assessed at both posttreatment Weeks 12 and 24 with 100% concordance between SVR12 and SVR24. Among subjects in the SOF+RBV 12 Week group, 122 had HCV RNA assessed at both posttreatment Weeks 12 and 24 with 100% concordance between SVR12 and SVR24.

	SOF/VEL 12 Weeks SVR24		SOF+RBV 12 Weeks SVR24		Overall SVR24	
	Yes (N = 127)	No (N = 0)	Yes (N = 122)	No (N = 0)	Yes (N = 249)	No (N = 2)
SVR12						
Yes	127	0	122	0	249	0
No	0	0	0	2	0	2
Positive Predictive Value	100%		100%		100%	

HCV RNA was analyzed using the COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with an LLOQ of 15 IU/mL.
Only subjects that had both posttreatment Week 12 and posttreatment Week 24 data were included in the analysis.
Source: Table 15.9.2.3

All efficacy analyses are provided in Tables 15.9.2.1.1 to 15.9.2.5 and Listings 16.2.6.1 to 16.2.6.4.

Full details on the resistance analysis are reported in Section 9.3.1 of the interim CSR (11 August 2015). No additional resistance analyses were performed since no subjects relapsed between posttreatment Week 12 and posttreatment Week 24.

Pharmacokinetic 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 (11 August 2105).

Adverse Events and Serious Adverse Events

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 AE resolution dates or minor clarifications to AE terms and newly reported Grade 1 or 2 AEs (Appendix 16.2, Listing 16.2.7.1 and Ad Hoc Listing 1). No additional treatment-emergent Grade 3 or 4 AEs were reported. These changes did not impact the overall interpretation or conclusions of the safety profile of SOF/VEL or SOF + RBV in this study. Ad Hoc Listing 1 provides a detailed listing of any newly reported AEs and AEs that had changes in reported or preferred term, onset date, or action(s) taken between the data cuts taken at the posttreatment Week 12 and posttreatment Week 24 time points.

No additional treatment-emergent SAEs were reported (Listing 16.2.7.4). No additional deaths were reported (Listing 16.2.7.3). Narratives for all SAEs, AEs leading to discontinuation of study drug, and deaths from the first dose of study drug through the end of the study (ie, the SVR24 visit) are provided in Section 15.2. No subject pregnancies were reported in this study (Listing 16.2.8.3).

All AE results are provided in Tables 15.11.2.1.1 to 15.11.5.6 and Listings 16.2.7.1 to 16.2.7.5.

Clinical Laboratory Results

Blood samples for clinical laboratory analyses were not collected at the posttreatment Week 24 visit. Overall, no clinically meaningful changes in the clinical laboratory results were observed (Tables 15.11.6.1.1 to 15.11.6.3, and Listings 16.2.8.1.3.1 to 16.2.8.1.9.

All laboratory results are provided in Tables 15.11.6.1.1 to 15.11.6.3 and Figures 15.11.6.1 to 15.11.6.10, and Listings 16.2.8.1.3.1 to 16.2.8.1.9.

Vital Sign Measurements and ECGs

Vital sign measurements (diastolic and systolic blood pressure, pulse, respiratory rate, and temperature) were collected at the posttreatment Week 24 visit. No notable changes were observed (Tables 15.11.7.1 to 15.11.7.3 and Listing 16.2.8.2.1).

All vital sign measurements and ECG results are provided in Tables 15.11.7.1 to 15.11.7.3 and 15.11.9, and Listings 16.2.8.2.1 and 16.2.8.2.3.1 to 16.2.8.2.3.2.

Quality of Life:

Full details on the quality of life questionnaires (SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hepatitis C) through posttreatment Week 4 are reported in Section 12 of the interim CSR (11 August 2015). All quality-of-life analyses are provided in Tables 15.12.1 to 15.12.4, Figures 15.12.1 to 15.12.4, and Listings 16.2.6.5 to 16.2.6.8.

Overall, results from the quality-of-life surveys remained consistent between posttreatment Week 12 and posttreatment Week 24 (Tables 15.12.1 to 15.12.4, Figures 15.12.1 to 15.12.4, and Listings 16.2.6.5 to 16.2.6.8). These results indicated that, in contrast to the RBV-free group (SOF/VEL), which had no decrements in quality-of-life from baseline to end-of-treatment, the RBV-containing group (SOF+RBV) had statistically significant ($p < 0.05$) worsening in health-related quality-of-life between baseline and EOT for the FACIT-F trial outcome index, and the WPAI: Hepatitis C percent activity impairment due to hepatitis C. The mean scores for most scales improved from end-of-treatment to 24 weeks after the end-of-treatment. These results should be interpreted with caution as multiple endpoints were tested, and the study was not powered to test these exploratory endpoints.

CONCLUSIONS:

The overall conclusions from this study are as follows:

- The study met its predefined primary efficacy endpoint, demonstrating that the SVR12 rate of 99.3% with SOF/VEL for 12 weeks was noninferior to the SVR12 rates of 93.9% with SOF+RBV for 12 weeks.
- Treatment with SOF/VEL for 12 weeks led to a statistically superior SVR12 rate compared with SOF+RBV for 12 weeks ($p = 0.018$).
- No SOF/VEL treated subjects or SOF+RBV treated subjects relapsed between posttreatment Weeks 12 and 24.
- No subjects treated with SOF/VEL experienced virologic failure.
- SOF/VEL was generally well tolerated and, compared with SOF+RBV, lacked toxicities associated with RBV. No treatment-emergent deaths, Grade 4 AEs, or clinically relevant laboratory abnormalities were observed.